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Social deprivation and unhealthy behavior related to major depression during pregnancy – a population-based analysis during 2002-2010 in Finland

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Keywords: Childbirth, Depression, Population Register, Register, Socioeconomic Status

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Abstract

Objectives: To identify predisposing factors for and the consequences of major depression during pregnancy treated in specialized healthcare, especially for women with no previous depression episodes.

Design: A population-based case-control study

Setting: Data was gathered from Finnish health registers for 2002-2010.

Participants: All singleton births (*n*=511,938)

Primary outcome measures: Prevalence, risk factors and consequences of major depression during pregnancy

Results: Among 511,938 women, 0.8% experienced major depression during pregnancy, of which 46.9% had a history of depression. After history of depression the second strongest associated factor for major depression was fear of childbirth, with a 2.6-fold (adjusted odds ratio (aOR2.63, 95% confidence interval (CI) 2.39-2.89) increased prevalence. The risk profile of major depression also included adolescent or advanced maternal age, low or unspecified socioeconomic status (SES), single marital status, smoking, prior pregnancy terminations, anemia and gestational diabetes regardless of a history of depression. Outcomes of pregnancies were worse among women with than without major depression. The contribution of smoking was substantial to modest for small for gestational age infants (< -2 standard deviation), low birth weight (< 2,500 g), preterm birth and admission to neonatal intensive care associated with major depression was, whereas SES made only a minor contribution.

Conclusions: Major depression during pregnancy was found to be rare and associated with social deprivation, lack of social support and unhealthy reproductive behavior such as smoking regardless

of a history of depression. Smoking during pregnancy made a substantial to modest contribution to adverse outcomes associated with depression during pregnancy.

Key words: Childbirth, Population Register, Depression, Register, Socioeconomic Status

Article summary

Article focus

- To identify predisposing factors for and the consequences of physician diagnosed major depression defined according to the International Classification of Diseases (ICD) - 10 codes during pregnancy, especially for women with no previous depression episodes.

Key messages

- After history of previous depression episode the strongest risk factor for major depression during pregnancy was physician-diagnosed fear of childbirth.

- Outcomes of pregnancies were worse among women with than without major depression.

Strengths and limitations

- Strengths of this study were the population-based data gathered from three mandatory national health registers, and physician-diagnosed depression defined by ICD-10 codes.

- Possible limitations were that we did not have information on women who experienced major depression during pregnancy and were diagnosed and treated in primary health care. Information on history of depression was based on outpatient and inpatient visits only since 1998 and 1996, respectively, and we did not have information on antidepressant medication at an individual level.

Introduction

Depression is globally one of the leading causes of disease burden for women (1). A previous large population-based study reported that 0.8% of 32.2 million women had physician-diagnosed depression at the time of delivery (2). A recent systematic review concluded that according to multivariable analyses, life stress, lack of social support and domestic violence were associated with an increased risk of depression during pregnancy, whereas maternal anxiety, history of depression, unintended pregnancy, lack of private medical insurance, low income, low education, smoking, single marital status and poor relationship were only significant predictors in bivariable analysis (3). The authors of the same review highlighted several limitations of previous studies, such as differences in the methods used to screen depression, study population, risk factors and confounders included in statistical analyses.

To date, only a few studies have evaluated the role of a history of depression as a predictor of antepartum depression, i.e., depression during pregnancy, but the association was not found to be statistically significant according to a multivariable analysis (3). Further, several previous studies have shown that diabetes mellitus, gestational diabetes (2,4), preeclampsia (2,5), anemia, caesarean section and placental abnormalities (2) are more prevalent among women suffering from perinatal depression.

Antepartum and postpartum depression represent a risk for children's short- and long-term wellbeing (6). Several studies have reported an association between antepartum depression and risk of preterm birth, but no association with other adverse outcomes, such as low birth weight, admission to a neonatal intensive care unit, preeclampsia and low Apgar scores (7). However, many of these studies were potentially underpowered because of small sample sizes and were also heterogeneous with respect to the study population and analyses. Further, the use of different methods to measure and define depression raises questions about whether all studies really

measured clinically diagnosed major depression (7). However, a recent large population-based study found that physician-diagnosed depression at the time of birth was associated with an increased prevalence of preterm birth, fetal growth restriction, fetal abnormalities, fetal distress and fetal death (2).

Using the same data we previously demonstrated that a history of depression and physician-diagnosed fear of childbirth were associated with an increased incidence of postpartum depression (8). The aim of the present study was to identify predisposing factors for major depression during pregnancy (International Classification of Diseases (ICD) -10 based) treated in specialized healthcare units, especially in women with no previous depression episodes. Furthermore, we studied whether major depression was associated with several neonatal outcomes and the degree to which this association was attenuated or mediated by women's SES and smoking during pregnancy in Finland.

Materials and Methods

Data and population

Data were gathered from three national health registers currently maintained by the National Institute for Health and Welfare and were linked using women's encrypted unique personal identification numbers. The Finnish MBR contains demographics, pregnancy and delivery characteristics and diagnoses on all live births or stillbirths delivered after the 22nd gestational week or weighing 500 g or more during the first postnatal week recorded since 1987. The MBR data was supplemented by information on maternal health gathered and defined based on ICD-10 codes from the Hospital Discharge Register (HDR) and the Congenital Malformations Register. The HDR was established in 1969 and contains information on all aspects of inpatient care and outpatient visits in Finnish hospitals. Data included all women with singleton births (*n*=511,938)

from 2002-2010; multiple births (*n*=15,767) were excluded because they carry a higher risk of complications.

The National Institute for Health and Welfare approved use of the data for the study as required by the national data protection legislation in Finland (Reference number 1749/5.05.00/2011).

Variables and definitions

Depression was defined by ICD-10 codes F31.3, F31.5 and F32-34 and women were grouped into four categories; 1) no depression either before or during pregnancy, 2) no depression during pregnancy, but a prior history of depression, 3) depression during pregnancy without a history of depression, and 4) depression during pregnancy with a history of depression. Information on depression was based on outpatient visits since 1998 and inpatient visits since 1996 gathered from the HDR. Parity was categorized as either nulliparous, if women had no prior births, or multiparous, if women had at least one prior birth. The gestational age was estimated based on first- or second-trimester ultrasonography measurements. Mode of delivery was classified as vaginal spontaneous, breech, forceps, vacuum assisted or caesarean section (CS). Smoking habits during pregnancy based on self-reported information was grouped into three categories: non-smoking, quitted smoking during the first trimester, and continued smoking after the first trimester, i.e., smoking. Marital status was classified as either married (including women living with a partner) or single. SES was grouped into five categories based on the Finnish Classification of Occupations (9), which was developed according to international recommendations: upper white-collar workers, such as physicians and lawyers; lower white-collar workers, such as nurses and secretaries; blue-collar workers, such as cooks and cashiers; others; and missing information, as categorized and published elsewhere (10). 'Others' comprised 25.9% (*n*=132,391) of all cases and included all births with unspecified occupations, such as entrepreneurs, students, retired, unemployed and housewives. The category with missing SES information comprised 17.4% (*n*=89,041) of all births. Information on

prior CS, induction, miscarriages and pregnancy terminations was dichotomous (yes or no). Information on in vitro fertilization (IVF) included intracytoplasmic sperm injection and frozen embryo transfers. Anemia was defined as hemoglobin levels ≤ 6.2 mmol/l. Placenta praevia, placental abruption, preeclampsia, gestational diabetes, and maternal diabetes mellitus were gathered from the HDR based on ICD-10 codes. Fear of childbirth was defined by national ICD-10 code O99.80. Feelings towards childbirth are asked all women in antenatal care and women experiencing significant fear of childbirth who cannot be counseled during antenatal visits in primary health care or making CS request due to fear of childbirth are referred to specialist maternity care (11).

Adverse perinatal outcomes: Admission to a neonatal intensive care unit was defined as at least 24 hour surveillance at neonatal intensive care. Stillbirth was defined as fetal death from 22 gestational weeks onwards and early neonatal death as death during the first seven postnatal days. Preterm birth was defined as gestational age <37+0 weeks. Low birth weight (LBW) was defined as a birth weight of less than 2,500 grams. Small for gestational age (SGA) was defined as a sex- and parity-specific birth weight more than two standard deviation (SD) below the mean weight for gestational based on the national 2013 population-based reference.(12) Five minute Apgar scores <7 and infant's vein pH < 7.15 were considered low (taken by indication and available since 2004).

Statistical analyses

Differences between the four categories of women defined by their depression history as described previously were evaluated by chi-square test for dichotomous or categorical variables and Kruskal-Wallis test for continuous variables. To understand correlates of major depression during pregnancy, two types of logistic models were fitted. In each, the outcome event of interest was major depression during pregnancy, but in the first type, the reference group was all women without major depression regardless of whether or not they had ever had a diagnosis of depression (i.e.,

categories 1 and 2), whereas in the second type, the reference group was restricted to women with neither current nor past history of major depression (i.e., category 1).

To address the second research aim regarding the contribution of major depression to neonatal outcomes with or without further control for smoking, SES and other covariates, a third set of models were fitted. For each neonatal outcome, a preliminary model (Model 1) was used to estimate the association between major depression and neonatal outcome. Then, additional covariates were added in subsequent models: adjustment for age and parity (Model 2), adjustment for Model 2 variables plus SES (Model 3), adjustment for Model 2 variables plus smoking (Model 4), and adjustment for all variables simultaneously (Model 5). Furthermore, multiple imputations were performed to study whether missing information on SES affected our results of logistic regression analysis. The data were analyzed using SPSS for Windows 19.0, Chicago, IL. Differences were deemed to be significant if $p < 0.05$. In addition, 95% confidence intervals (CIs) were calculated.

Results

In total, 0.8% (n=4,120) of 511,938 women with singleton pregnancy suffered from major depression during pregnancy as diagnosed by ICD-10 codes in specialized healthcare units. Of all the women with major depression during pregnancy, 53.1% (2,189 of 4,120) did not have a history of depression before pregnancy. Table 1 shows demographics, delivery characteristics and reproductive factors for women with and without major depression during pregnancy according to their history of depression. Women who suffered from major depression during pregnancy were more frequently nulliparous, younger, and gave birth by caesarean section, to a male infant, and had a lower mean birth weight compared with women with no depression. Further, they more frequently were smokers, of unspecified SES and had reproductive risk factors, such as prior pregnancy terminations, anemia, major congenital anomalies, gestational diabetes and maternal diabetes

mellitus, and suffered more frequently from fear of childbirth compared with women with no depression.

Table 2 shows risk factors for major depression during pregnancy using women with no antepartum depression (categories 1 and 2) as a reference population. The strongest risk factors for major depression during pregnancy were a history of depression and fear of childbirth, which were associated with a 22.4- and 2.6-fold increased prevalence of major depression during pregnancy, respectively. An increased prevalence of major depression during pregnancy was also associated with adolescent and advanced maternal age, smoking during pregnancy, single marital status, prior pregnancy terminations of pregnancy, low or unspecified SES, anemia and gestational diabetes. Table 3 shows group specific risk factors separately for women without or with a history of depression using women with no depression (category 1) as a reference population. The strongest predisposing factor for major depression during pregnancy was fear of childbirth, which increased the prevalence of antepartum depression by about four- to five-fold among both groups. Group specific risk factors were almost identical to those of the total population presented in Table 2. Multiple data imputations of missing SES information did not change the results (data not shown).

Pregnancies of women who suffered from major depression during pregnancy more frequently resulted in adverse perinatal outcomes, such as, stillbirth, preterm birth, LBW, SGA, Apgar scores <7 at 5 minute, fetal venous pH <7.15 at birth, admission to a neonatal intensive care unit and major congenital anomalies, compared with women without major depression during pregnancy (Table 4). Major depression was not associated with early neonatal death. Smoking appeared to contribute the most to the increased prevalence of SGA, LBW, preterm birth, stillbirth and admission to a neonatal intensive care associated with major depression, but made only a minor contribution to the increased prevalence of other perinatal outcomes (major congenital anomalies, Apgar scores <7 at 5 minute), except early neonatal death and low fetal venous pH, associated with major depression

during pregnancy. SES made a minor contribution to the increased prevalence of all perinatal outcomes, except admission to a neonatal unit, early neonatal death and low fetal venous pH, associated with major depression during pregnancy.

Discussion

Main findings

The prevalence of major depression during pregnancy among women with singleton births was 0.8%, which is consistent with a previous population- and diagnosis-based study (2), but substantially lower than 3.1-12.8% reported by smaller studies utilizing mostly self-reported screening or interviews (13-15). It should be noted that we did not include cases where depression during pregnancy was diagnosed and treated in primary healthcare units or non-diagnosed cases. More than half of the episodes occurred in women without a history of depression, but predisposing antenatal risk factors were similar regardless of the history of depression. The second strongest associated factor for major depression during pregnancy after history of depression was fear of childbirth, which was associated with three-fold increased odds of major depression during pregnancy. Major depression during pregnancy occurred most frequently in women with low or unspecified SES, single marital status and unhealthy behavior, such as smoking. Outcomes of pregnancies were substantially worse than in women with no major depression during pregnancy. Smoking during pregnancy contributed substantially to an increased prevalence of SGA, LBW, preterm birth and admission to a neonatal unit associated with major depression during pregnancy.

Strengths and limitations

The present study has several strengths: the data included the entire childbearing population gathered from three national health registers with high-quality data (16,17), depression during

pregnancy was diagnosed by a physician, analyses were performed separately for women with and without a history of depression and some novel risk factors, such as fear of childbirth, were studied. However, we acknowledge several limitations with the present study. Information on depression covered only cases diagnosed and treated in specialized medical care units. We did not have information on women who experienced major depression during pregnancy and were diagnosed and treated in primary health care. Further, information on depression was available only since 1996 for inpatient visits and since 1998 for outpatient visits, and therefore we may not have had complete information on all pre-pregnancy depression episodes. In addition, we had no information on antidepressant medication at an individual level and history of adverse pregnancy outcomes, and thus could not assess their roles as confounders in the multivariable analyses. Further, information on SES could not be defined or was missing for approximately 40% of the births. SES is self-reported and optional, and due to confidentiality concerns, a large number of women chose not provide it. However, the socio-demographics of this group were close to those of the general population, and multiple data imputations of missing information did not change the results (data not shown). Further, SES was solely defined based on maternal occupation at birth that is related to education and income in Finland, and is an appropriate available indicator for studies on socioeconomic health disparity (18,19). Further, due to data protection issues we did not have information on spouses' SES. No adjustment was made for multiple comparisons, and model results should be interpreted accordingly.

Interpretation

History of depression was the strongest predisposing factor for major depression during pregnancy. However, more than half of the women with major depression during pregnancy had no history of depression indicating that the first episode of depression is not uncommon during pregnancy. Otherwise, risk factors for major depression during pregnancy did not vary substantially between

women with and without a history of depression. We showed that social disparity, lack of social support, and unhealthy reproductive behavior, such as smoking, were predisposing factors for major depression during pregnancy. These results are partly in line with a previous systematic review suggesting that smoking, anxiety symptoms, lower SES, life stress, and lack of social support were associated with an increased prevalence of antepartum depression (3). Further, the association between gestational diabetes and maternal diabetes mellitus was in accordance with the results of previous studies (2,4). However, our results did not confirm the association between preeclampsia and perinatal depression found in previous studies (2,5). In general, it has been suggested that depression and other pregnancy morbidities, such as diabetes and preeclampsia, would have a partially common physiological pathway (20).

Our results showed that outcomes of pregnancies affected by major depression during pregnancy were worse than pregnancies not affected by major depression during pregnancy. It seemed that smoking mediated the association between adverse perinatal outcomes and depression during pregnancy. However, whether there is causation between smoking and depression and how these are linked, i.e., whether depression leads to smoking or smoking alters the risk of depression, could not be concluded based on the present evidence. A limitation of the present study was that we could not assess the contribution of antidepressant medication to adverse perinatal outcomes associated with depression during pregnancy, since we did not have access to this information on an individual level. Among the total delivering population, the use of selective serotonin reuptake inhibitors (SSRIs) ranged from 0.5% in 1997 to 3.7% in 2010 in Finland. Based on previous systematic reviews and meta-analysis, antidepressant medication during pregnancy has been shown to be associated with preterm birth (21), lower Apgar scores (21) and poor neonatal adaptation (22), but not with major congenital anomalies (23). Further, exposure specifically to SSRIs has been shown

to be associated with preterm birth (24) and low Apgar scores (25), but not with stillbirth, neonatal mortality or postnatal mortality (26).

Conclusions

Using a large 9-year national population of all singleton births, we concluded that physician-diagnosed episodes of major depression in specialized healthcare units during pregnancy were rare, and unexpectedly more than half of the episodes occurred in women with no previous depressive episodes. Predisposing factors for major depression during pregnancy were social deprivation, lack of social support and unhealthy behavior during pregnancy, such as smoking and fear of childbirth, regardless of the history of depression. This result may help clinicians to recognize the risk of depression. Outcomes of pregnancies among women affected by major depression during pregnancy were worse than in unaffected women, but smoking during pregnancy made a substantial or modest contribution to the increased prevalence of SGA, LBW, preterm and admission to a neonatal unit associated with depression during pregnancy. Smoking and social disparity seemed to be clustered to women with major antepartum depression. Therefore, because of possible severe maternal and fetal consequences and high risk of relapse, treatment of antepartum depression should be managed actively by a multi-professional team.

Ethical approval

Permission to use the confidential register data in this study was approved on 16th February, 2012 by the National Institute for Health and Welfare (THL) in Finland. (Reference number 1749/5.05.00/2011).

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Competing interests: None.

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Data sharing: No additional data available.

Contributor statement

All authors participated in designing the study. SR managed the dataset and performed statistical analyses. SML, HSN, MG, MRK and SH were statistical advisors. All authors contributed to the interpretation of the results, as well as to writing and editing the manuscript.

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Table 1. Delivery characteristics and reproductive risk factors among women with singleton pregnancies with and without major depression during pregnancy and with and without a history of depression from 2002 to 2010 in Finland.

% or mean (SD)	No major depression during pregnancy, *n*=493,037 (96.3%)	No major depression during pregnancy, *n*= 14,781 (2.9%)	Major depression during pregnancy, *n*=2,189 (0.4%)	Major depression during pregnancy, *n*=1,931 (0.4%)	*p value**
History of depression	No	Yes	No	Yes	
Nulliparous	42.0	45.1	45.5	50.0	*≤0.001*
Multiparous	58.0	54.9	54.5	50.0	
Mean maternal age, years (SD)	29.6 (5.4)	27.6 (6.0)	28.4 (6.2)	28.7 (6.6)	≤0.001
Mean gestational age, wk (SD)	39.8 (1.8)	39.7 (1.9)	39.4 (2.0)	39.5 (2.0)	≤0.001
Mode of delivery %					≤0.001
Vaginal spontaneous	75.8	74.8	72.6	70.4	
Breech	0.6	0.6	0.2	0.4	
Forceps	0.1	0.1	0.1	0.0	
Vacuum assistance	7.2	7.5	7.5	7.7	
Caesarean section	15.9	17.1	19.6	21.5	
Mean birth weight, g (SD)	3531.4 (550)	3479.0 (568)	3453.1 (580)	3456.3 (608)	≤0.001
Male sex %	51.2	50.0	51.1	51.8	0.04
Induction %	16.6	19.6	19.4	22.3	≤0.001
Smoking status					
Non-smoking	83.2	63.4	66.1	59.5	≤0.001
Quit smoking during 1st trimester	3.7	6.9	6.5	8.3	
Smoking after 1st trimester	10.5	26.7	25.1	29.3	
Missing	2.6	2.9	2.3	3.0	
Married or living with a partner	93.5	86.3	83.1	83.0	≤0.001
Socioeconomic status					
Upper white-collar worker	8.6	3.7	4.0	3.8	≤0.001
Lower white-collar worker	34.5	25.8	27.9	25.5	
Blue-collar worker	14.2	16.0	14.9	15.3	
Others [a]	25.7	31.0	31.9	30.0	
Missing information	17.2	23.6	21.3	25.3	
Prior miscarriages	20.7	23.6	23.3	23.2	≤0.001
Prior terminations	12.2	22.4	19.8	21.7	≤0.001
In vitro fertilization	1.6	1.2	0.9	1.3	≤0.001
Anemia Hgb ≤ 6.2 mmol/l	1.6	2.6	3.5	2.8	≤0.001
Chorionic villus biopsy	1.0	1.2	1.1	1.5	0.04
Amniocentesis	2.5	2.2	2.3	3.3	0.02
Placenta praevia	0.3	0.2	0.2	0.4	0.54
Placental abruption	0.3	0.4	0.5	0.7	0.07
Major congenital anomalies	4.0	5.2	5.6	5.9	≤0.001
Preeclampsia	1.2	1.3	0.9	1.2	0.52
Gestational diabetes	11.2	13.4	14.5	17.6	≤0.001
Maternal diabetes mellitus	8.4	10.9	11.6	13.6	≤0.001
Prior caesarean section	10.6	10.5	10.3	10.2	0.90
Fear of childbirth	4.6	11.4	15.0	17.5	≤0.001

SD=standard deviation, *chi-square or Kruskal-Wallis test, [a] 'Others' comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases,

Table 2. Adjusted odds ratios (aOR) of major depression during pregnancy among women with singleton pregnancies (*n*=491,520) from 2002-2010 in Finland using women with no major depression during pregnancy as a reference population.

	Major depression during pregnancy
n	3,842
Characteristic	aOR (95% CI)
Depression before pregnancy	22.36 (20.86-23.98)
Maternal age (years)	
≤19	1.58 (1.38-1.81)
20–29	1
30–39	1.19 (1.11-1.28)
≥40	1.65 (1.41-1.94)
Nulliparous women	1.21 (1.12-1.30)
Multiparous women	1
Smoking status	
Non-smoking	1
Quit smoking during 1st trimester	1.57 (1.38-1.80)
Smoking after 1st trimester	1.67 (1.53-1.81)
Missing information	1.09 (0.88-1.35)
Married/living with a partner	1
Single	1.63 (1.48-1.79)
Socioeconomic status	
Upper white-collar worker	1
Lower white-collar worker	1.42 (1.20-1.69)
Blue-collar worker	1.53 (1.27-1.84)
Others [a]	1.67 (1.40-1.98)
Missing information	1.66 (1.39-1.98)
Prior miscarriages	1.09 (1.00-1.18)
Prior terminations	1.14 (1.04-1.24)
In vitro fertilization	0.78 (0.58-1.07)
Anemia ≤100 g/L	1.49 (1.22-1.81)
Gestational diabetes	1.29 (1.11-1.50)
Maternal diabetes mellitus	1.10 (0.93-1.31)
Fear of childbirth	2.63 (2.39-2.89)
Male fetal sex	0.97 (0.91-1.04)

[a] Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases, CI=confidence interval

Table 3. Adjusted odds ratios (aOR) of major depression during pregnancy among women with singleton pregnancies with and without a history of depression from 2002-2010 in Finland using women with no major depression during pregnancy and no history of depression as a reference group for both analyses.

	Major depression during pregnancy without a history of depression	Major depression during pregnancy with a history of depression
n	2,044	1,798
Characteristic	aOR (95% CI)	aOR (95% CI)
Maternal age (years)		
≤19	1.77 (1.46-2.13)	1.88 (1.56-2.27)
20–29	1	1
30–39	0.96 (0.87-1.06)	1.01 (0.91-1.13)
≥40	1.20 (0.96-1.50)	1.66 (1.34-2.06)
Nulliparous women	1.09 (0.99-1.20)	1.35 (1.22-1.50)
Multiparous women	1	1
Smoking status		
Non-smoking	1	1
Quit smoking during 1st trimester	1.75 (1.45-2.11)	2.59 (2.17-3.08)
Smoking after 1st trimester	2.25 (2.01-2.52)	2.97 (2.64-3.33)
Missing information	0.99 (0.72-1.34)	1.50 (1.13-1.99)
Married/living with a partner	1	1
Single	2.08 (1.84-2.35)	1.84 (1.62-2.10)
Socioeconomic status		
Upper white-collar worker	1	1
Lower white-collar worker	1.60 (1.26-2.01)	1.43 (1.11-1.83)
Blue-collar worker	1.72 (1.34-2.21)	1.66 (1.27-2.17)
Others [a]	2.17 (1.72-2.73)	1.98 (1.54-2.55)
Missing information	2.02 (1.59-2.57)	2.43 (1.88-3.13)
Prior miscarriages	1.20 (1.08-1.33)	1.18 (1.05-1.32)
Prior terminations	1.35 (1.20-1.51)	1.44 (1.28-1.61)
In vitro fertilization	0.71 (0.46-1.11)	0.94 (0.62-1.41)
Anemia ≤100 g/L	2.03 (1.60-2.59)	1.45 (1.08-1.95)
Gestational diabetes	1.09 (0.88-1.36)	1.52 (1.23-1.87)
Maternal diabetes mellitus	1.33 (1.04-1.68)	1.20 (0.95-1.51)
Fear of childbirth	3.80 (3.36-4.29)	4.61 (4.07-5.21)
Male fetal sex	1.00 (0.92-1.09)	0.97 (0.89-1.07)

[a] Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases, CI=confidence interval

Table 4. Adjusted odds ratios (ORs) of characteristics and risk factors associated with adverse perinatal outcomes among singleton births in Finland from 2002-2010.

Perinatal outcome	**Model 1** adjusted by major depression during pregnancy	**Model 2** adjusted by Model 1 + age and parity	**Model 3**adjusted by Model 2 + socioeconomic status (SES)	**Model 4** adjusted by Model 2 + smoking	**Model 5** adjusted by Model 2 + SES and smoking
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Admission to a NICU	1.79 (1.65-1.95)	1.78 (1.64-1.94)	1.78 (1.64-1.93)	1.68 (1.55-1.83)	1.69 (1.55-1.84)
Stillbirth	1.97 (1.33-2.93)	2.01 (1.35-2.99)	1.86 (1.25-2.76)	1.88 (1.27-2.80)	1.77 (1.19-2.63)
Early neonatal death	1.08 (0.49-2.42)	1.13 (0.50-2.51)			
Preterm birth (<37 weeks)	1.57 (1.39-1.77)	1.57 (1.39-1.77)	1.55 (1.37-1.75)	1.49 (1.32-1.68)	1.48 (1.31-167)
LBW (<2500 g)	1.56 (1.36-1.79)	1.55 (1.35-1.79)	1.53 (1.33-1.76)	1.37 (1.19-1.58)	1.36 (1.18-1.56)
SGA (<-2 SD)	1.46 (1.27-1.67)	1.41 (1.23-1.62)	1.39 (1.21-1.59)	1.18 (1.03-1.36)	1.17 (1.02-1.35)
Apgar scores (<7 at 5 minute) [a]	2.13 (1.79-2.54)	2.11 (1.77-2.51)	2.07 (1.74-2.47)	2.05 (1.72-2.45)	2.02 (1.70-2.41)
Fetal venous pH <7.15 at birth [a, b]	1.37 (1.06-1.76)	1.32 (1.03-1.71)	1.33 (1.03-1.72)	1.35 (1.05-1.74)	1.36 (1.06-1.76)
Major congenital anomaly	1.47 (1.29-1.67)	1.48 (1.29-1.69)	1.47 (1.29-1.68)	1.44 (1.26-1.65)	1.44 (1.26-1.64)

[a] available since 2004, [b] gathered selectively by indication, NICU= neonatal intensive care unit, LBW= low birth weight, SGA= small for gestational age

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
D **Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **OK**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **OK**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **OK**
Objectives	3	State specific objectives, including any prespecified hypotheses **OK**
Methods		
Study design	4	Present key elements of study design early in the paper **OK**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **OK**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **OK**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **NA**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **OK**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **OK**
Bias	9	Describe any efforts to address potential sources of bias **OK**
Study size	10	Explain how the study size was arrived at **TOTAL POPULATION**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **OK**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **OK**
		(*b*) Describe any methods used to examine subgroups and interactions **OK**
		(*c*) Explain how missing data were addressed **OK**
		(*d*) If applicable, explain how loss to follow-up was addressed **NO**
		(*e*) Describe any sensitivity analyses **OK**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **OK**
		(b) Give reasons for non-participation at each stage **NO**
		(c) Consider use of a flow diagram **NA**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **OK**
		(b) Indicate number of participants with missing data for each variable of interest **OK**
		(c) Summarise follow-up time (eg, average and total amount) **OK**
Outcome data	15*	Report numbers of outcome events or summary measures over time **OK**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included **OK**
		(*b*) Report category boundaries when continuous variables were categorized OK
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **OK**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **OK**
Discussion		
Key results	18	Summarise key results with reference to study objectives **OK**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **OK**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **OK**
Generalisability	21	Discuss the generalisability (external validity) of the study results **OK**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **OK**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Low socioeconomic status and unhealthy behavior related to major depression during pregnancy – a population-based analysis during 2002-2010 in Finland

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Low socioeconomic status and unhealthy behavior related to major depression during pregnancy – a population-based analysis during 2002-2010 in Finland

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Abstract

Objectives: To identify predisposing factors for and the consequences (several adverse perinatal outcomes) of physician-diagnosed major depression during pregnancy treated in specialized healthcare.

Design: A population-based cross sectional study

Setting: Data were gathered from Finnish health registers for 1996-2010.

Participants: All singleton births (*n*=511,938) for 2002-2010 in Finland

Primary outcome measures: Prevalence, risk factors and consequences of major depression during pregnancy

Results: Among 511,938 women, 0.8% experienced major depression during pregnancy, of which 53.1% had a history of depression prior to pregnancy. After history of depression the second strongest associated factor for major depression was fear of childbirth, with a 2.6-fold (adjusted odds ratio (aOR=2.63, 95% confidence interval (CI)=2.39-2.89) increased prevalence. The risk profile of major depression also included adolescent or advanced maternal age, low or unspecified socioeconomic status (SES), single marital status, smoking, prior pregnancy terminations, anaemia and gestational diabetes regardless of a history of depression. Outcomes of pregnancies were worse among women with than without major depression. The contribution of smoking was substantial to modest for small for gestational age newborn (< -2 standard deviation below mean birth), low birth weight (< 2,500 g), preterm birth (<37 weeks) and admission to neonatal intensive care associated with major depression was, whereas SES made only a minor contribution.

Conclusions: Major depression during pregnancy was found to be rare and associated with low SES, lack of social support and unhealthy reproductive behavior such as smoking regardless of a

history of depression prior to pregnancy. Outcomes of pregnancies were worse among women with than without major depression. Smoking during pregnancy made a substantial to modest contribution to adverse outcomes associated with depression during pregnancy.

Key words: Childbirth, Population Register, Depression, Register, Socioeconomic Status

Article summary

Article focus

- To identify predisposing factors for and the consequences of physician-diagnosed major depression during pregnancy defined according to the International Classification of Diseases (ICD) - 10 codes during pregnancy.

Key messages

- After history of depression prior to pregnancy the strongest risk factor for major depression during pregnancy was physician-diagnosed fear of childbirth.

- Outcomes of pregnancies were worse among women with than without major depression.

Strengths and limitations

- Strengths of this study were the population-based data gathered from three mandatory national health registers, and physician-diagnosed depression defined by ICD-10 codes.

- Possible limitations were that we did not have information on women diagnosed and treated for major depression during pregnancy in primary health care, information on history of depression was based on outpatient and inpatient visits only since 1998 and 1996, respectively, and we did not have information on antidepressant medication at an individual level.

Introduction

Depression is globally one of the leading causes of disease burden for women (1). A previous large population-based study reported that 0.8% of 32.2 million women had physician-diagnosed depression at the time of delivery in United States (US) during 1998-2005 (2). A recent systematic review concluded that according to multivariable analyses, life stress, lack of social support and domestic violence were associated with an increased risk of depression during pregnancy, whereas maternal anxiety, history of depression, unintended pregnancy, lack of private medical insurance, low income, low education, smoking, single marital status and poor relationship were only significant predictors in bivariable analysis (3). The authors of this review highlighted several limitations of previous studies, such as differences in the methods used to screen depression, study population, risk factors and confounders included in statistical analyses.

To date, only a few studies have evaluated the role of a history of depression as a predictor of antepartum depression, i.e., depression during pregnancy, but the association was not found to be statistically significant according to a multivariable analysis (3). Further, several previous studies have shown that diabetes mellitus, gestational diabetes (2,4), preeclampsia (2,5), anaemia, caesarean section and placental abnormalities (2) are more prevalent among women suffering from perinatal depression.

Antepartum and postpartum depression represent a risk for children's short- and long-term wellbeing (6). Several studies have reported an association between antepartum depression and risk of preterm birth, but no association with other adverse outcomes, such as low birth weight, admission to a neonatal intensive care unit, preeclampsia and low Apgar scores, as shownin a systematic review and meta-analysis (7). However, many of these studies were potentially underpowered because of small sample sizes and were also heterogeneous with respect to the study population and analyses. Further, the use of different methods to measure and define depression

raises questions about whether all studies really measured clinically diagnosed major depression (7). Further, the previous mentioned large population-based study from US found that physician-diagnosed depression at the time of birth was associated with an increased prevalence of preterm birth, fetal growth restriction, fetal abnormalities, fetal distress and fetal death (2).

The aim of the present large population based cross sectional study was to identify predisposing factors for major depression during pregnancy (International Classification of Diseases (ICD) -10 based) treated in specialized healthcare units, especially an association between a prior history of depression and antepartum depression that was only studied by few smaller studies (3). Furthermore, we studied whether major depression during pregnancy was associated with adverse perinatal outcomes and the degree to which this association was attenuated or mediated by women's SES and smoking during pregnancy in Finland. Most previous studies considering an association between adverse perinatal outcomes and depression were small and population based studies were scarce (7). Further, differences in health care services such as access to antenatal care might limit generalizability of the large previous study from US (2). In Finland, with around 5.5 million residents, health care services are mainly publicly funded and all women have free access to antenatal care.

Materials and Methods

Data and population

Data were gathered from three national health registers currently maintained by the National Institute for Health and Welfare and were linked using women's encrypted unique personal identification numbers. The Finnish MBR contains demographics, pregnancy and delivery characteristics and diagnoses on all live births or stillbirths delivered after the 22nd gestational week or weighing 500 g or more during the first postnatal week recorded since 1987. The MBR

data was supplemented by information on maternal health (major depression, preeclampsia, gestational diabetes, pre-existing diabetes, and fear of childbirth) gathered and defined based on ICD-10 codes from the Hospital Discharge Register (HDR). The HDR was established in 1969 and contains information on all aspects of inpatient care and outpatient visits in Finnish hospitals. Information on major congenital anomalies (yes or no) was gathered and the Register of Congenital Malformations established 1963. Data included all women with singleton births (*n*=511,938) from 2002-2010; multiple births (*n*=15,767) were excluded because they carry a higher risk of complications. The present time period was chosen since information on depression (i.e., a history of depression prior to pregnancy) was available since 1996 for inpatient visits and since 1998 for outpatient visits.

The National Institute for Health and Welfare approved study plan and use of the data for the study as required by the national data protection legislation in Finland (Reference number 1749/5.05.00/2011).

Variables and definitions

Depression, physician-diagnosed, was defined by ICD-10 codes F31.3, F31.5 and F32-34 and women were grouped into four categories; 1) no major depression during pregnancy, and no history of depression prior to pregnancy, 2) no major depression during pregnancy with a history of depression prior to pregnancy, 3) major depression during pregnancy with no history of depression prior to pregnancy, and 4) major depression during pregnancy with a history of depression prior to pregnancy. Information on major depression was based on outpatient visits (patients without overnight hospitalization) in specialized health care since 1998 and inpatient visits (at least an overnight stay at a hospital) specialized health care since 1996 gathered from the HDR. In Finland, general practitioners and midwives in health care centers provide primary health care such as antenatal care, and specialists in regional and university teaching hospitals provide specialized

health care. Health care professionals at both levels are instructed to evaluate the mother's mental wellbeing as part of all appointments. Parity was categorized as either nulliparous, if women had no prior births, or multiparous, if women had at least one prior birth. The gestational age was estimated based on first- or second-trimester ultrasonography measurements. Mode of delivery was classified as vaginal spontaneous, breech, forceps, vacuum assisted or caesarean section (CS). Smoking habits during pregnancy based on self-reported information was grouped into three categories: non-smoking, quitted smoking during the first trimester, and continued smoking after the first trimester, i.e., smoking. Marital status was classified as either married (including women living with a partner) or single. SES was grouped into five categories based on the Finnish Classification of Occupations (8), which was developed according to international recommendations: upper white-collar workers, such as physicians and lawyers; lower white-collar workers, such as nurses and secretaries; blue-collar workers, such as cooks and cashiers; others; and missing information, as categorized and published elsewhere (9). 'Others' comprised 25.9% (*n*=132,391) of all cases and included all births with unspecified occupations, such as entrepreneurs, students, retired, unemployed and housewives. The category with missing SES information comprised 17.4% (*n*=89,041) of all births. Information on prior CS, induction, miscarriages and pregnancy terminations was dichotomous (yes or no). Information on in vitro fertilization (IVF) included intracytoplasmic sperm injection and frozen embryo transfers. Anaemia was defined as hemoglobin levels ≤100 g/L. Placenta praevia (O44), placental abruption (O45), preeclampsia (O14 and O15), gestational diabetes (O24.4), and maternal preexisting diabetes (O24.0 and O24.1) were gathered from the HDR based on ICD-10 codes. Fear of childbirth was defined by national ICD-10 code O99.80. Feelings towards childbirth are asked all women in antenatal care and women experiencing significant fear of childbirth who cannot be counseled during antenatal visits in primary health care or making CS request due to fear of childbirth are referred to specialist maternity care as described previously (10,11).

Adverse perinatal outcomes: Admission to a neonatal intensive care unit (NICU) was defined as at least 24 hour surveillance at neonatal intensive care. Stillbirth was defined as fetal death from 22 gestational weeks onwards or birth weight 500 grams or more and early neonatal death as death during the first seven postnatal days. Preterm birth was defined as gestational age < 37+0 weeks. Low birth weight (LBW) was defined as a birth weight of less than 2,500 grams. Small for gestational age (SGA) was defined as a sex- and parity-specific birth weight more than two standard deviation (SD) below the mean weight for gestational based on the national 2013 population-based reference (12) Five minute Apgar scores < 7 and infant's vein pH < 7.15 were considered low (taken by indication and available since 2004).

Statistical analyses

Differences between the four categories of women defined by their depression history as described previously were evaluated by chi-square test for dichotomous or categorical variables and Kruskal-Wallis test for continuous variables. To understand correlates of major depression during pregnancy, two types of logistic models were fitted. In first type of model the outcome event of interest was major depression during pregnancy (categories 3 and 4), and the reference group was all women without major depression without or with a history of depression prior to pregnancy (categories 1 and 2). In second type of model the outcome event of interest was women with major depression with no history of depression prior to pregnancy (category 3), and the reference group was all women without major depression with no history of depression prior to pregnancy (category 1), or the outcome event of interest was women with major depression with a history of depression prior to pregnancy (category 4), and the reference group was all women without major depression without or with a history of depression prior to pregnancy (categories 1 and 2). Unadjusted and adjusted odds ratios (ORs) of major depression were determined by using logistic regression analyses. All covariates were determined based on literature and results of bivariable analyses.

To address the second research aim regarding the contribution of major depression to adverse perinatal outcomes with or without further control for smoking, SES and other covariates, a third set of models were fitted. For each perinatal outcome, a preliminary model (Model 1) was used to estimate the association between major depression and neonatal outcome. Then, additional covariates were added in subsequent models: adjustment for age and parity (Model 2), adjustment for Model 2 variables plus SES (Model 3), adjustment for Model 2 variables plus smoking (Model 4), and adjustment for all variables simultaneously (Model 5). Furthermore, multiple imputations were performed to study whether missing information on SES affected our results of logistic regression analysis. The data were analyzed using SPSS for Windows 19.0, Chicago, IL. Differences were deemed to be significant if $p < 0.05$. In addition, 95% confidence intervals (CIs) were calculated.

Results

In total, 0.8% (*n*=4,120) of 511,938 women with singleton pregnancy suffered from major depression during pregnancy as diagnosed by ICD-10 codes in specialized healthcare units. Of all the women with major depression during pregnancy, 53.1% (2,189 of 4,120) did not have a history of depression prior to pregnancy. Table 1 shows demographics, delivery characteristics and reproductive factors for women with and without major depression during pregnancy according to their history of depression prior to pregnancy. Women who suffered from major depression during pregnancy were more frequently nulliparous, younger, and gave birth by caesarean section, to a male infant, and had a lower mean birth weight compared with women with no depression during pregnancy. Further, they more frequently were smokers, of unspecified SES and had reproductive risk factors, such as prior pregnancy terminations, anaemia, major congenital anomalies, gestational diabetes and maternal pre-existing diabetes, and suffered more frequently from fear of childbirth compared with women with no major depression during pregnancy.

Table 2 shows risk factors for major depression during pregnancy (categories 3 and 4) using women with no major depression without or with a history of depression prior to pregnancy (categories 1 and 2) as a reference population. The strongest risk factors for major depression during pregnancy were a history of depression prior to pregnancy and fear of childbirth, which were associated with a 22.4- and 2.6-fold increased prevalence of major depression during pregnancy, respectively. An increased prevalence of major depression during pregnancy was also associated with adolescent and advanced maternal age, smoking during pregnancy, single marital status, prior pregnancy terminations of pregnancy, low or unspecified SES, anaemia and gestational diabetes. Table 3 shows group specific risk factors for women with major depression without (category 3) and with a history of depression prior to pregnancy (category 4) using women with no major depression without a history of depression prior to pregnancy (category 1), and women with no major depression without or with a history of depression prior to pregnancy (categories 1 and 2) as reference populations, respectively. The strongest predisposing factor for major depression during pregnancy was fear of childbirth, which increased the prevalence of antepartum depression by about four-fold among both groups. Group specific risk factors were almost identical to those of the total population presented in Table 2. We performed all the analyses using multiple imputed data, but the results did not change (data not shown).

Pregnancies of women who suffered from major depression during pregnancy more frequently resulted in adverse perinatal outcomes, such as, stillbirth, preterm birth, LBW, SGA, Apgar scores < 7 at 5 minute, fetal venous pH < 7.15 at birth, admission to a neonatal intensive care unit and major congenital anomalies, compared with women without major depression during pregnancy (Table 4). Major depression was not associated with early neonatal death. Smoking appeared to contribute the most to the increased prevalence of SGA, LBW, preterm birth, stillbirth and admission to a neonatal intensive care associated with major depression, but made only a minor

contribution to the increased prevalence of other perinatal outcomes, except early neonatal death and low fetal venous pH, associated with major depression during pregnancy. SES made a minor contribution to the increased prevalence of all perinatal outcomes, except admission to a neonatal unit, early neonatal death and low fetal venous pH, associated with major depression during pregnancy.

Discussion

Main findings

The prevalence of major depression during pregnancy among women with singleton births was 0.8%, which is consistent with a previous population- and diagnosis-based study (2), but substantially lower than 3.1-12.8% reported by smaller studies utilizing mostly self-reported screening or interviews (13-15). More than half of the episodes occurred in women without a history of depression prior to pregnancy, but predisposing antenatal risk factors were similar regardless of the history of depression. The second strongest associated factor for major depression during pregnancy after history of depression was fear of childbirth, which was associated with three-fold increased odds of major depression during pregnancy. Major depression during pregnancy occurred most frequently in women with low or unspecified SES, single marital status and unhealthy behavior, such as smoking. Outcomes of pregnancies were substantially worse than in women with no major depression during pregnancy. Smoking during pregnancy contributed substantially to an increased prevalence of SGA, LBW, preterm birth and admission to a neonatal unit associated with major depression during pregnancy.

Strengths and limitations

The present study has several strengths: the data included the entire childbearing population gathered from three national health registers with high-quality data (16,17) depression during pregnancy was diagnosed by a physician, analyses were performed separately for women with and without a history of depression and some novel risk factors, such as fear of childbirth, were studied. However, we acknowledge several limitations with the present study. Information on depression covered only cases diagnosed and treated in specialized medical care units. We did not have information on women experienced major depression during pregnancy diagnosed treated in primary health care. However, it is likely that most high-risk pregnancies such as women with diagnosed depression were treated in by specialized maternity care, thus providing us information on most women with major depression. Further, information on depression was available only since 1996 for inpatient visits and since 1998 for outpatient visits, and therefore we may not have had complete information on all pre-pregnancy depression episodes. In addition, we had no information on antidepressant medication at an individual level and history of adverse pregnancy outcomes, and thus could not assess their roles as confounders in the multivariable analyses. Further, information on SES could not be defined or was missing for approximately 40% of the births. SES is self-reported and optional, and due to confidentiality concerns, a large number of women chose not provide it. However, the socio-demographics of this group were close to those of the general population, and multiple data imputations of missing information did not change the results (data not shown). Further, SES was solely defined based on maternal occupation at birth that is related to education and income in Finland, and is an appropriate available indicator for studies on socioeconomic health disparity (18,19). Further, due to data protection issues we did not have information on spouses' SES. No adjustment was made for multiple comparisons, and model results should be interpreted accordingly.

Interpretation

History of depression prior to pregnancy was the strongest predisposing factor for major depression during pregnancy. However, more than half of the women with major depression during pregnancy had no history of depression indicating that the first episode of depression is not uncommon during pregnancy. A previous systematic review (3) did not report a positive association between a history of depression prior to pregnancy and antenatal depression, but there were only three studies with multivariable analyses. The three previous studies were with small sample size and had heterogeneity in assessment for a prior history of depression (3). A novel finding of the present study was that physician-diagnosed fear of childbirth was associated with on the order of three-fold increased prevalence of major depression during pregnancy. Several previous studies reported an association between anxiety disorders and major depression during pregnancy as previously reviewed (3). Otherwise, risk factors for major depression during pregnancy did not vary substantially between women with and without a history of depression. We showed that low SES, lack of social support, and unhealthy reproductive behavior, such as smoking, were predisposing factors for major depression during pregnancy. These results are partly in line with a previous systematic review suggesting that smoking, anxiety symptoms, lower SES, life stress, and lack of social support were associated with an increased prevalence of antepartum depression (3). Further, the association between gestational diabetes and maternal pre-existing diabetes was in accordance with the results of previous studies (2,4). However, our results did not confirm the association between preeclampsia and perinatal depression found in previous studies (2,5). In general, it has been suggested that depression and other pregnancy morbidities, such as diabetes and preeclampsia, would have a partially common physiological pathway (20).

Our results showed that outcomes of pregnancies affected by major depression during pregnancy were worse than pregnancies not affected by major depression during pregnancy. Several previous studies reviewed found a positive association between preterm birth and depression during

pregnancy, but not with other outcomes such as LBW, Apgar scores and admission to NICU (7). However, the authors suggest that the results might be affected by differences in definition of perinatal outcomes (many studies did not use standard definitions), and that many studies were underpowered or did not have all important covariates such as maternal smoking (7).

It seemed that smoking mediated the association between adverse perinatal outcomes and depression during pregnancy. However, whether there is causation between smoking and depression and how these are linked, i.e., whether depression leads to smoking or smoking alters the risk of depression, could not be concluded based on the present evidence. A limitation of the present study was that we could not assess the contribution of antidepressant medication to adverse perinatal outcomes associated with depression during pregnancy, since we did not have access to this information on an individual level. Among the total delivering population, the use of selective serotonin reuptake inhibitors (SSRIs) ranged from 0.5% in 1997 to 3.7% in 2010 in Finland. Based on previous systematic reviews and meta-analysis, antidepressant medication during pregnancy has been shown to be associated with preterm birth (21), lower Apgar scores (21) and poor neonatal adaptation (22), but not with major congenital anomalies (23). Further, exposure specifically to SSRIs has been shown to be associated with preterm birth (24) and low Apgar scores (25), but not with stillbirth, neonatal mortality or postnatal mortality (26).

Conclusions

Using a large 9-year national population of all singleton births, we concluded that physician-diagnosed episodes of major depression in specialized healthcare units during pregnancy were rare, and unexpectedly more than half of the episodes occurred in women with no previous depressive episodes. Predisposing factors for major depression during pregnancy were low SES, lack of social support and unhealthy behavior during pregnancy, such as smoking and fear of childbirth, regardless of the history of depression. This result may help clinicians to recognize the risk of

depression. Outcomes of pregnancies among women affected by major depression during pregnancy were worse than in unaffected women, but smoking during pregnancy made a substantial or modest contribution to the increased prevalence of SGA, LBW, preterm and admission to a neonatal unit associated with depression during pregnancy. Furthermore, its of note that women with history of depression prior to pregnancy or major depression during pregnancy are more likely to experience postpartum depression (27), and consequences of postpartum depression might be more severe for women, since it has shown to be associated with an increased risk of self-harm such as suicide (28,29). Therefore, because of possible severe maternal and fetal consequences and high risk of relapse, treatment of antepartum depression should be managed actively by a multi-professional team.

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Contributor statement

All authors participated in designing the study. SR managed the dataset and performed statistical analyses. SML, HSN, MG, MRK and SH were statistical advisors. All authors contributed to the interpretation of the results, as well as to writing and editing the manuscript

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Table 1. Delivery characteristics and reproductive risk factors among women with singleton pregnancies with and without major depression during pregnancy and with and without a history of depression prior to pregnancy from 2002 to 2010 in Finland.

Characteristic	No major depression during pregnancy, *n*=493,037 (96.3%)	No major depression during pregnancy, *n*= 14,781 (2.9%)	Major depression during pregnancy, *n*=2,189 (0.4%)	Major depression during pregnancy, *n*=1,931 (0.4%)	*p value**
A history of depression prior to pregnancy	No	Yes	No	Yes	
Nulliparous % Multiparous	42.0 58.0	45.1 54.9	45.5 54.5	50.0 50.0	*≤0.001*
Mean maternal age, years (SD)	29.6 (5.4)	27.6 (6.0)	28.4 (6.2)	28.7 (6.6)	≤0.001
Mean gestational age, wk (SD)	39.8 (1.8)	39.7 (1.9)	39.4 (2.0)	39.5 (2.0)	≤0.001
Mode of delivery % Vaginal spontaneous Breech Forceps Vacuum assistance Caesarean section	 75.8 0.6 0.1 7.2 15.9	 74.8 0.6 0.1 7.5 17.1	 72.6 0.2 0.1 7.5 19.6	 70.4 0.4 0.0 7.7 21.5	≤0.001
Mean birth weight, g (SD)	3531.4 (550)	3479.0 (568)	3453.1 (580)	3456.3 (608)	≤0.001
Male fetal sex %	51.2	50.0	51.1	51.8	0.04
Major congenital anomalies %	4.0	5.2	5.6	5.9	≤0.001
Smoking status % Non-smoking Quit smoking during 1st trimester Smoking after 1st trimester Missing information	 83.2 3.7 10.5 2.6	 63.4 6.9 26.7 2.9	 66.1 6.5 25.1 2.3	 59.5 8.3 29.3 3.0	≤0.001
Married or living with a partner %	93.5	86.3	83.1	83.0	≤0.001
Socioeconomic status % Upper white-collar worker Lower white-collar worker Blue-collar worker Others [a] Missing information	 8.6 34.5 14.2 25.7 17.2	 3.7 25.8 16.0 31.0 23.6	 4.0 27.9 14.9 31.9 21.3	 3.8 25.5 15.3 30.0 25.3	≤0.001
Prior miscarriages %	20.7	23.6	23.3	23.2	≤0.001
Prior terminations %	12.2	22.4	19.8	21.7	≤0.001
In vitro fertilization (IVF) %	1.6	1.2	0.9	1.3	≤0.001
Anaemia, ≤100 g/L %	1.6	2.6	3.5	2.8	≤0.001
Placenta praevia %	0.3	0.2	0.2	0.4	0.54
Placental abruption %	0.3	0.4	0.5	0.7	0.07
Preeclampsia %	1.2	1.3	0.9	1.2	0.52
Gestational diabetes %	11.2	13.4	14.5	17.6	≤0.001
Pre-existing diabetes %	8.4	10.9	11.6	13.6	≤0.001
Prior caesarean section %	10.6	10.5	10.3	10.2	0.90
Fear of childbirth %	4.6	11.4	15.0	17.5	≤0.001

SD=standard deviation, *chi-square or Kruskal-Wallis test, [a] 'Others' comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases,

Table 2. Unadjusted and adjusted odds ratios (aOR) of major depression during pregnancy among women with singleton pregnancies from 2002-2010 in Finland using women with no major depression during pregnancy without and with a history of depression prior to pregnancy as a reference population (categories 1 and 2).

Characteristic	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)
A history of depression prior to pregnancy	29.43 (27.62-31.35)	22.36 (20.86-23.98)
Maternal age (years)		
≤19	3.14 (2.79-3.52)	1.58 (1.38-1.81)
20–29	1	1
30–39	0.86 (0.81-0.92)	1.19 (1.11-1.28)
≥40	1.41 (1.22-1.63)	1.65 (1.41-1.94)
Nulliparous women	1.25 (1.18-1.33)	1.21 (1.12-1.30)
Multiparous women	1	1
Smoking status		
Non-smoking	1	1
Quit smoking during 1st trimester	2.52 (2.23-2.84)	1.57 (1.38-1.80)
Smoking after 1st trimester	3.25 (3.03-3.49)	1.67 (1.53-1.81)
Missing information	1.32 (1.09-1.60)	1.09 (0.88-1.35)
Married/living with a partner	1	1
Single	2.86 (2.62-3.11)	1.63 (1.48-1.79)
Socioeconomic status		
Upper white-collar worker	1	1
Lower white-collar worker	1.69 (1.43-1.99)	1.42 (1.20-1.69)
Blue-collar worker	2.29 (1.93-2.73)	1.53 (1.27-1.84)
Others [a]	2.59 (2.20-3.05)	1.67 (1.40-1.98)
Missing information	2.88 (2.43-3.40)	1.66 (1.39-1.98)
Prior miscarriages	1.15 (1.07-1.24)	1.09 (1.00-1.18)
Prior terminations	1.82 (1.69-1.97)	1.14 (1.04-1.24)
In vitro fertilization (IVF)	0.70 (0.53-0.94)	0.78 (0.58-1.07)
Anaemia ≤100 g/L	2.02 (1.70-2.41)	1.49 (1.22-1.81)
Gestational diabetes	1.49 (1.37-1.62)	1.29 (1.11-1.50)
Pre-existing diabetes	1.56 (1.42-1.71)	1.10 (0.93-1.31)
Fear of childbirth	3.80 (3.49-4.13)	2.63 (2.39-2.89)
Male fetal sex	1.01 (0.95-1.07)	0.97 (0.91-1.04)

*ORs of major depression adjusted by history of depression prior to pregnancy, maternal age, parity, smoking status, marital status, SES, prior miscarriages, prior terminations, IVF, anaemia, gestational diabetes, pre-existing diabetes, fear of childbirth, and fetal sex.

[a] Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases, CI=confidence interval

Table 3. Unadjusted and adjusted odds ratios (OR) of major depression during pregnancy separately for women without (category 3) and with a history of depression prior to pregnancy (category 4) among women with singleton pregnancies from 2002-2010 in Finland using women without major depression without a history of depression prior to pregnancy (category 1) [a] and women without major depression without and with a history of depression prior to pregnancy (categories 1 and 2) [b] as reference groups.

Characteristic	Major depression during pregnancy without a history of depression prior to pregnancy [a]		Major depression during pregnancy with a history of depression prior to pregnancy [b]	
	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)
Maternal age (years)				
≤19	3.02 (2.57-3.56)	1.77 (1.46-2.13)	3.42 (2.90-4.03)	1.86 (1.55-2.24)
20–29	1	1	1	1
30–39	0.85 (0.77-0.93)	0.96 (0.87-1.06)	0.87 (0.79-0.96)	1.04 (0.93-1.15)
≥40	1.21 (0.98-1.49)	1.20 (0.96-1.50)	1.63 (1.34-1.99)	1.70 (1.37-2.10)
Nulliparous women	1.15 (1.06-1.26)	1.09 (0.99-1.20)	1.38 (1.26-1.51)	1.35 (1.22-1.50)
Multiparous women	1	1	1	1
Smoking status				
Non-smoking	1	1	1	1
Quit smoking during 1st trimester	2.19 (1.84-2.61)	1.75 (1.45-2.11)	3.03 (2.55-3.56)	2.51 (2.11-2.99)
Smoking after 1st trimester	3.02 (2.74-3.34)	2.25 (2.01-2.52)	3.72 (3.36-4.12)	2.83 (2.52-3.17)
Missing information	1.13 (0.85-1.49)	0.99 (0.72-1.34)	1.57 (1.20-2.05)	1.49 (1.12-1.98)
Married/living with a partner	1	1	1	1
Single	2.94 (2.62-3.30)	2.08 (1.84-2.35)	2.87 (2.53-3.24)	1.80 (1.58-2.05)
Socioeconomic status				
Upper white-collar worker	1	1	1	1
Lower white-collar worker	1.75 (1.39-2.19)	1.60 (1.26-2.01)	1.64 (1.28-2.09)	1.42 (1.11-1.83)
Blue-collar worker	2.27 (1.79-2.88)	1.72 (1.34-2.21)	2.37 (1.84-3.06)	1.66 (1.27-2.16)
Others [c]	2.68 (2.14-3.35)	2.17 (1.72-2.73)	2.56 (2.01-3.26)	1.94 (1.51-2.50)
Missing information	2.67 (2.13-3.36)	2.02 (1.59-2.57)	3.20 (2.51-4.09)	2.36 (1.83-3.04)
Prior miscarriages	1.16 (1.05-1.28)	1.20 (1.08-1.33)	1.15 (1.04-1.28)	1.17 (1.04-1.31)
Prior terminations	1.77 (1.59-1.97)	1.35 (1.20-1.51)	1.94 (1.74-2.16)	1.41 (1.25-1.58)
In vitro fertilization	0.57 (0.37-0.89)	0.71 (0.46-1.11)	0.85 (0.58-1.26)	0.93 (0.62-1.41)
Anaemia ≤100 g/L	2.28 (1.81-2.86)	2.03 (1.60-2.59)	1.79 (1.36-2.34)	1.41 (1.05-1.90)
Gestational diabetes	1.34 (1.19-1.51)	1.09 (0.88-1.36)	1.67 (1.49-1.88)	1.53 (1.24-1.88)
Pre-existing diabetes	1.44 (1.26-1.64)	1.33 (1.04-1.68)	1.71 (1.50-1.95)	1.18 (0.94-1.49)
Fear of childbirth	3.64 (3.23-4.09)	3.80 (3.36-4.29)	4.16 (3.70-4.68)	4.35 (3.85-4.92)
Male fetal sex	0.99 (0.91-1.08)	1.00 (0.92-1.09)	0.98 (0.89-1.07)	1.03 (0.94-1.13)

*ORs of major depression during pregnancy adjusted by maternal age, parity, smoking status, marital status, SES, prior miscarriages, prior terminations, IVF, anaemia, gestational diabetes, pre-existing diabetes, fear of childbirth, and fetal sex.

[c] Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases, CI=confidence interval

Table 4. Adjusted odds ratios (ORs) of major depression during pregnancy associated with adverse perinatal outcomes among singleton births in Finland from 2002-2010.

Perinatal outcome	**Model 1** adjusted by major depression during pregnancy	**Model 2** adjusted by Model 1 + age and parity	**Model 3**adjusted by Model 2 + socioeconomic status (SES)	**Model 4** adjusted by Model 2 + smoking	**Model 5** adjusted by Model 2 + SES and smoking
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Admission to a NICU	1.79 (1.65-1.95)	1.78 (1.64-1.94)	1.78 (1.64-1.93)	1.68 (1.55-1.83)	1.69 (1.55-1.84)
Stillbirth	1.97 (1.33-2.93)	2.01 (1.35-2.99)	1.86 (1.25-2.76)	1.88 (1.27-2.80)	1.77 (1.19-2.63)
Early neonatal death	1.08 (0.49-2.42)	1.13 (0.50-2.51)			
Preterm birth (<37 weeks)	1.57 (1.39-1.77)	1.57 (1.39-1.77)	1.55 (1.37-1.75)	1.49 (1.32-1.68)	1.48 (1.31-167)
LBW (<2500 grams)	1.56 (1.36-1.79)	1.55 (1.35-1.79)	1.53 (1.33-1.76)	1.37 (1.19-1.58)	1.36 (1.18-1.56)
SGA (<-2 SD below mean birth weight)	1.46 (1.27-1.67)	1.41 (1.23-1.62)	1.39 (1.21-1.59)	1.18 (1.03-1.36)	1.17 (1.02-1.35)
Apgar scores (<7 at 5 minute) [a]	2.13 (1.79-2.54)	2.11 (1.77-2.51)	2.07 (1.74-2.47)	2.05 (1.72-2.45)	2.02 (1.70-2.41)
Fetal venous pH <7.15 at birth [a, b]	1.37 (1.06-1.76)	1.32 (1.03-1.71)	1.33 (1.03-1.72)	1.35 (1.05-1.74)	1.36 (1.06-1.76)
Major congenital anomaly	1.47 (1.29-1.67)	1.48 (1.29-1.69)	1.47 (1.29-1.68)	1.44 (1.26-1.65)	1.44 (1.26-1.64)

[a] available since 2004, [b] gathered selectively by indication, NICU= neonatal intensive care unit, LBW= low birth weight, SGA= small for gestational age, CI=confidence interval, SD=standard deviation

Low socioeconomic status and unhealthy behavior related to major depression during pregnancy – a population-based analysis during 2002-2010 in Finland

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Keywords: Childbirth, Depression, Population Register, Register, Socioeconomic Status

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Abstract

Objectives: To identify predisposing factors for and the consequences (several adverse perinatal outcomes) of physician-diagnosed major depression during pregnancy treated in specialized healthcare.

Design: A population-based cross sectional study

Setting: Data were gathered from Finnish health registers for 1996-2010.

Participants: All singleton births (*n*=511,938) for 2002-2010 in Finland

Primary outcome measures: Prevalence, risk factors and consequences of major depression during pregnancy

Results: Among 511,938 women, 0.8% experienced major depression during pregnancy, of which 53.1% had a history of depression prior to pregnancy. After history of depression the second strongest associated factor for major depression was fear of childbirth, with a 2.6-fold (adjusted odds ratio (aOR=2.63, 95% confidence interval (CI)=2.39-2.89) increased prevalence. The risk profile of major depression also included adolescent or advanced maternal age, low or unspecified socioeconomic status (SES), single marital status, smoking, prior pregnancy terminations, anaemia and gestational diabetes regardless of a history of depression. Outcomes of pregnancies were worse among women with than without major depression. The contribution of smoking was substantial to modest for small for gestational age newborn (< -2 standard deviation below mean birth), low birth weight (< 2,500 g), preterm birth (<37 weeks) and admission to neonatal intensive care associated with major depression was, whereas SES made only a minor contribution.

Conclusions: Major depression during pregnancy was found to be rare and associated with low SES, lack of social support and unhealthy reproductive behavior such as smoking regardless of a

history of depression prior to pregnancy. Outcomes of pregnancies were worse among women with than without major depression. Smoking during pregnancy made a substantial to modest contribution to adverse outcomes associated with depression during pregnancy.

Key words: Childbirth, Population Register, Depression, Register, Socioeconomic Status

Article summary

Article focus

- To identify predisposing factors for and the consequences of physician-diagnosed major depression during pregnancy defined according to the International Classification of Diseases (ICD) - 10 codes during pregnancy.

Key messages

- After history of depression prior to pregnancy the strongest risk factor for major depression during pregnancy was physician-diagnosed fear of childbirth.

- Outcomes of pregnancies were worse among women with than without major depression.

Strengths and limitations

- Strengths of this study were the population-based data gathered from three mandatory national health registers, and physician-diagnosed depression defined by ICD-10 codes.

- Possible limitations were that we did not have information on women diagnosed and treated for major depression during pregnancy in primary health care, information on history of depression was based on outpatient and inpatient visits only since 1998 and 1996, respectively, and we did not have information on antidepressant medication at an individual level.

Introduction

Depression is globally one of the leading causes of disease burden for women (1). A previous large population-based study reported that 0.8% of 32.2 million women had physician-diagnosed depression at the time of delivery in United States (US) during 1998-2005 (2). A recent systematic review concluded that according to multivariable analyses, life stress, lack of social support and domestic violence were associated with an increased risk of depression during pregnancy, whereas maternal anxiety, history of depression, unintended pregnancy, lack of private medical insurance, low income, low education, smoking, single marital status and poor relationship were only significant predictors in bivariable analysis (3). The authors of this review highlighted several limitations of previous studies, such as differences in the methods used to screen depression, study population, risk factors and confounders included in statistical analyses.

To date, only a few studies have evaluated the role of a history of depression as a predictor of antepartum depression, i.e., depression during pregnancy, but the association was not found to be statistically significant according to a multivariable analysis (3). Further, several previous studies have shown that diabetes mellitus, gestational diabetes (2,4), preeclampsia (2,5), anaemia, caesarean section and placental abnormalities (2) are more prevalent among women suffering from perinatal depression.

Antepartum and postpartum depression represent a risk for children's short- and long-term wellbeing (6). Several studies have reported an association between antepartum depression and risk of preterm birth, but no association with other adverse outcomes, such as low birth weight, admission to a neonatal intensive care unit, preeclampsia and low Apgar scores, as shownin a systematic review and meta-analysis (7). However, many of these studies were potentially underpowered because of small sample sizes and were also heterogeneous with respect to the study population and analyses. Further, the use of different methods to measure and define depression

raises questions about whether all studies really measured clinically diagnosed major depression (7). Further, the previous mentioned large population-based study from US found that physician-diagnosed depression at the time of birth was associated with an increased prevalence of preterm birth, fetal growth restriction, fetal abnormalities, fetal distress and fetal death (2).

The aim of the present large population based cross sectional study was to identify predisposing factors for major depression during pregnancy (International Classification of Diseases (ICD) -10 based) treated in specialized healthcare units, especially an association between a prior history of depression and antepartum depression that was only studied by few smaller studies (3). Furthermore, we studied whether major depression during pregnancy was associated with adverse perinatal outcomes and the degree to which this association was attenuated or mediated by women's SES and smoking during pregnancy in Finland. Most previous studies considering an association between adverse perinatal outcomes and depression were small and population based studies were scarce (7). Further, differences in health care services such as access to antenatal care might limit generalizability of the large previous study from US (2). In Finland, with around 5.5 million residents, health care services are mainly publicly funded and all women have free access to antenatal care.

Materials and Methods

Data and population

Data were gathered from three national health registers currently maintained by the National Institute for Health and Welfare and were linked using women's encrypted unique personal identification numbers. The Finnish MBR contains demographics, pregnancy and delivery characteristics and diagnoses on all live births or stillbirths delivered after the 22nd gestational week or weighing 500 g or more during the first postnatal week recorded since 1987. The MBR

data was supplemented by information on maternal health (major depression, preeclampsia, gestational diabetes, pre-existing diabetes, and fear of childbirth) gathered and defined based on ICD-10 codes from the Hospital Discharge Register (HDR). The HDR was established in 1969 and contains information on all aspects of inpatient care and outpatient visits in Finnish hospitals. Information on major congenital anomalies (yes or no) was gathered and the Register of Congenital Malformations established 1963. Data included all women with singleton births (*n*=511,938) from 2002-2010; multiple births (*n*=15,767) were excluded because they carry a higher risk of complications. The present time period was chosen since information on depression (i.e., a history of depression prior to pregnancy) was available since 1996 for inpatient visits and since 1998 for outpatient visits.

The National Institute for Health and Welfare approved study plan and use of the data for the study as required by the national data protection legislation in Finland (Reference number 1749/5.05.00/2011).

Variables and definitions

Depression, physician-diagnosed, was defined by ICD-10 codes F31.3, F31.5 and F32-34 and women were grouped into four categories; 1) no major depression during pregnancy, and no history of depression prior to pregnancy, 2) no major depression during pregnancy with a history of depression prior to pregnancy, 3) major depression during pregnancy with no history of depression prior to pregnancy, and 4) major depression during pregnancy with a history of depression prior to pregnancy. Information on major depression was based on outpatient visits (patients without overnight hospitalization) in specialized health care since 1998 and inpatient visits (at least an overnight stay at a hospital) specialized health care since 1996 gathered from the HDR. In Finland, general practitioners and midwives in health care centers provide primary health care such as antenatal care, and specialists in regional and university teaching hospitals provide specialized

health care. Health care professionals at both levels are instructed to evaluate the mother's mental wellbeing as part of all appointments. Parity was categorized as either nulliparous, if women had no prior births, or multiparous, if women had at least one prior birth. The gestational age was estimated based on first- or second-trimester ultrasonography measurements. Mode of delivery was classified as vaginal spontaneous, breech, forceps, vacuum assisted or caesarean section (CS). Smoking habits during pregnancy based on self-reported information was grouped into three categories: non-smoking, quitted smoking during the first trimester, and continued smoking after the first trimester, i.e., smoking. Marital status was classified as either married (including women living with a partner) or single. SES was grouped into five categories based on the Finnish Classification of Occupations (8), which was developed according to international recommendations: upper white-collar workers, such as physicians and lawyers; lower white-collar workers, such as nurses and secretaries; blue-collar workers, such as cooks and cashiers; others; and missing information, as categorized and published elsewhere (9). 'Others' comprised 25.9% (*n*=132,391) of all cases and included all births with unspecified occupations, such as entrepreneurs, students, retired, unemployed and housewives. The category with missing SES information comprised 17.4% (*n*=89,041) of all births. Information on prior CS, induction, miscarriages and pregnancy terminations was dichotomous (yes or no). Information on in vitro fertilization (IVF) included intracytoplasmic sperm injection and frozen embryo transfers. Anaemia was defined as hemoglobin levels ≤100 g/L. Placenta praevia (O44), placental abruption (O45), preeclampsia (O14 and O15), gestational diabetes (O24.4), and maternal preexisting diabetes (O24.0 and O24.1) were gathered from the HDR based on ICD-10 codes. Fear of childbirth was defined by national ICD-10 code O99.80. Feelings towards childbirth are asked all women in antenatal care and women experiencing significant fear of childbirth who cannot be counseled during antenatal visits in primary health care or making CS request due to fear of childbirth are referred to specialist maternity care as described previously (10,11).

Adverse perinatal outcomes: Admission to a neonatal intensive care unit (NICU) was defined as at least 24 hour surveillance at neonatal intensive care. Stillbirth was defined as fetal death from 22 gestational weeks onwards or birth weight 500 grams or more and early neonatal death as death during the first seven postnatal days. Preterm birth was defined as gestational age < 37+0 weeks. Low birth weight (LBW) was defined as a birth weight of less than 2,500 grams. Small for gestational age (SGA) was defined as a sex- and parity-specific birth weight more than two standard deviation (SD) below the mean weight for gestational based on the national 2013 population-based reference (12) Five minute Apgar scores < 7 and infant's vein pH < 7.15 were considered low (taken by indication and available since 2004).

Statistical analyses

Differences between the four categories of women defined by their depression history as described previously were evaluated by chi-square test for dichotomous or categorical variables and Kruskal-Wallis test for continuous variables. To understand correlates of major depression during pregnancy, two types of logistic models were fitted. In first type of model the outcome event of interest was major depression during pregnancy (categories 3 and 4), and the reference group was all women without major depression without or with a history of depression prior to pregnancy (categories 1 and 2). In second type of model the outcome event of interest was women with major depression with no history of depression prior to pregnancy (category 3), and the reference group was all women without major depression with no history of depression prior to pregnancy (category 1), or the outcome event of interest was women with major depression with a history of depression prior to pregnancy (category 4), and the reference group was all women without major depression without or with a history of depression prior to pregnancy (categories 1 and 2). Unadjusted and adjusted odds ratios (ORs) of major depression were determined by using logistic regression analyses. All covariates were determined based on literature and results of bivariable analyses.

To address the second research aim regarding the contribution of major depression to adverse perinatal outcomes with or without further control for smoking, SES and other covariates, a third set of models were fitted. For each perinatal outcome, a preliminary model (Model 1) was used to estimate the association between major depression and neonatal outcome. Then, additional covariates were added in subsequent models: adjustment for age and parity (Model 2), adjustment for Model 2 variables plus SES (Model 3), adjustment for Model 2 variables plus smoking (Model 4), and adjustment for all variables simultaneously (Model 5). Furthermore, multiple imputations were performed to study whether missing information on SES affected our results of logistic regression analysis. The data were analyzed using SPSS for Windows 19.0, Chicago, IL. Differences were deemed to be significant if $p < 0.05$. In addition, 95% confidence intervals (CIs) were calculated.

Results

In total, 0.8% (*n*=4,120) of 511,938 women with singleton pregnancy suffered from major depression during pregnancy as diagnosed by ICD-10 codes in specialized healthcare units. Of all the women with major depression during pregnancy, 53.1% (2,189 of 4,120) did not have a history of depression prior to pregnancy. Table 1 shows demographics, delivery characteristics and reproductive factors for women with and without major depression during pregnancy according to their history of depression prior to pregnancy. Women who suffered from major depression during pregnancy were more frequently nulliparous, younger, and gave birth by caesarean section, to a male infant, and had a lower mean birth weight compared with women with no depression during pregnancy. Further, they more frequently were smokers, of unspecified SES and had reproductive risk factors, such as prior pregnancy terminations, anaemia, major congenital anomalies, gestational diabetes and maternal pre-existing diabetes, and suffered more frequently from fear of childbirth compared with women with no major depression during pregnancy.

Table 2 shows risk factors for major depression during pregnancy (categories 3 and 4) using women with no major depression without or with a history of depression prior to pregnancy (categories 1 and 2) as a reference population. The strongest risk factors for major depression during pregnancy were a history of depression prior to pregnancy and fear of childbirth, which were associated with a 22.4- and 2.6-fold increased prevalence of major depression during pregnancy, respectively. An increased prevalence of major depression during pregnancy was also associated with adolescent and advanced maternal age, smoking during pregnancy, single marital status, prior pregnancy terminations of pregnancy, low or unspecified SES, anaemia and gestational diabetes. Table 3 shows group specific risk factors for women with major depression without (category 3) and with a history of depression prior to pregnancy (category 4) using women with no major depression without a history of depression prior to pregnancy (category 1), and women with no major depression without or with a history of depression prior to pregnancy (categories 1 and 2) as reference populations, respectively. The strongest predisposing factor for major depression during pregnancy was fear of childbirth, which increased the prevalence of antepartum depression by about four-fold among both groups. Group specific risk factors were almost identical to those of the total population presented in Table 2. We performed all the analyses using multiple imputed data, but the results did not change (data not shown).

Pregnancies of women who suffered from major depression during pregnancy more frequently resulted in adverse perinatal outcomes, such as, stillbirth, preterm birth, LBW, SGA, Apgar scores < 7 at 5 minute, fetal venous pH < 7.15 at birth, admission to a neonatal intensive care unit and major congenital anomalies, compared with women without major depression during pregnancy (Table 4). Major depression was not associated with early neonatal death. Smoking appeared to contribute the most to the increased prevalence of SGA, LBW, preterm birth, stillbirth and admission to a neonatal intensive care associated with major depression, but made only a minor

contribution to the increased prevalence of other perinatal outcomes, except early neonatal death and low fetal venous pH, associated with major depression during pregnancy. SES made a minor contribution to the increased prevalence of all perinatal outcomes, except admission to a neonatal unit, early neonatal death and low fetal venous pH, associated with major depression during pregnancy.

Discussion

Main findings

The prevalence of major depression during pregnancy among women with singleton births was 0.8%, which is consistent with a previous population- and diagnosis-based study (2), but substantially lower than 3.1-12.8% reported by smaller studies utilizing mostly self-reported screening or interviews (13-15). More than half of the episodes occurred in women without a history of depression prior to pregnancy, but predisposing antenatal risk factors were similar regardless of the history of depression. The second strongest associated factor for major depression during pregnancy after history of depression was fear of childbirth, which was associated with three-fold increased odds of major depression during pregnancy. Major depression during pregnancy occurred most frequently in women with low or unspecified SES, single marital status and unhealthy behavior, such as smoking. Outcomes of pregnancies were substantially worse than in women with no major depression during pregnancy. Smoking during pregnancy contributed substantially to an increased prevalence of SGA, LBW, preterm birth and admission to a neonatal unit associated with major depression during pregnancy.

Strengths and limitations

The present study has several strengths: the data included the entire childbearing population gathered from three national health registers with high-quality data (16,17) depression during pregnancy was diagnosed by a physician, analyses were performed separately for women with and without a history of depression and some novel risk factors, such as fear of childbirth, were studied. However, we acknowledge several limitations with the present study. Information on depression covered only cases diagnosed and treated in specialized medical care units. We did not have information on women experienced major depression during pregnancy diagnosed treated in primary health care. However, it is likely that most high-risk pregnancies such as women with diagnosed depression were treated in by specialized maternity care, thus providing us information on most women with major depression. Further, information on depression was available only since 1996 for inpatient visits and since 1998 for outpatient visits, and therefore we may not have had complete information on all pre-pregnancy depression episodes. In addition, we had no information on antidepressant medication at an individual level and history of adverse pregnancy outcomes, and thus could not assess their roles as confounders in the multivariable analyses. Further, information on SES could not be defined or was missing for approximately 40% of the births. SES is self-reported and optional, and due to confidentiality concerns, a large number of women chose not provide it. However, the socio-demographics of this group were close to those of the general population, and multiple data imputations of missing information did not change the results (data not shown). Further, SES was solely defined based on maternal occupation at birth that is related to education and income in Finland, and is an appropriate available indicator for studies on socioeconomic health disparity (18,19). Further, due to data protection issues we did not have information on spouses' SES. No adjustment was made for multiple comparisons, and model results should be interpreted accordingly.

Interpretation

History of depression prior to pregnancy was the strongest predisposing factor for major depression during pregnancy. However, more than half of the women with major depression during pregnancy had no history of depression indicating that the first episode of depression is not uncommon during pregnancy. A previous systematic review (3) did not report a positive association between a history of depression prior to pregnancy and antenatal depression, but there were only three studies with multivariable analyses. The three previous studies were with small sample size and had heterogeneity in assessment for a prior history of depression (3). A novel finding of the present study was that physician-diagnosed fear of childbirth was associated with on the order of three-fold increased prevalence of major depression during pregnancy. Several previous studies reported an association between anxiety disorders and major depression during pregnancy as previously reviewed (3). Otherwise, risk factors for major depression during pregnancy did not vary substantially between women with and without a history of depression. We showed that low SES, lack of social support, and unhealthy reproductive behavior, such as smoking, were predisposing factors for major depression during pregnancy. These results are partly in line with a previous systematic review suggesting that smoking, anxiety symptoms, lower SES, life stress, and lack of social support were associated with an increased prevalence of antepartum depression (3). Further, the association between gestational diabetes and maternal pre-existing diabetes was in accordance with the results of previous studies (2,4). However, our results did not confirm the association between preeclampsia and perinatal depression found in previous studies (2,5). In general, it has been suggested that depression and other pregnancy morbidities, such as diabetes and preeclampsia, would have a partially common physiological pathway (20).

Our results showed that outcomes of pregnancies affected by major depression during pregnancy were worse than pregnancies not affected by major depression during pregnancy. Several previous studies reviewed found a positive association between preterm birth and depression during

pregnancy, but not with other outcomes such as LBW, Apgar scores and admission to NICU (7). However, the authors suggest that the results might be affected by differences in definition of perinatal outcomes (many studies did not use standard definitions), and that many studies were underpowered or did not have all important covariates such as maternal smoking (7).

It seemed that smoking mediated the association between adverse perinatal outcomes and depression during pregnancy. However, whether there is causation between smoking and depression and how these are linked, i.e., whether depression leads to smoking or smoking alters the risk of depression, could not be concluded based on the present evidence. A limitation of the present study was that we could not assess the contribution of antidepressant medication to adverse perinatal outcomes associated with depression during pregnancy, since we did not have access to this information on an individual level. Among the total delivering population, the use of selective serotonin reuptake inhibitors (SSRIs) ranged from 0.5% in 1997 to 3.7% in 2010 in Finland. Based on previous systematic reviews and meta-analysis, antidepressant medication during pregnancy has been shown to be associated with preterm birth (21), lower Apgar scores (21) and poor neonatal adaptation (22), but not with major congenital anomalies (23). Further, exposure specifically to SSRIs has been shown to be associated with preterm birth (24) and low Apgar scores (25), but not with stillbirth, neonatal mortality or postnatal mortality (26).

Conclusions

Using a large 9-year national population of all singleton births, we concluded that physician-diagnosed episodes of major depression in specialized healthcare units during pregnancy were rare, and unexpectedly more than half of the episodes occurred in women with no previous depressive episodes. Predisposing factors for major depression during pregnancy were low SES, lack of social support and unhealthy behavior during pregnancy, such as smoking and fear of childbirth, regardless of the history of depression. This result may help clinicians to recognize the risk of

depression. Outcomes of pregnancies among women affected by major depression during pregnancy were worse than in unaffected women, but smoking during pregnancy made a substantial or modest contribution to the increased prevalence of SGA, LBW, preterm and admission to a neonatal unit associated with depression during pregnancy. Furthermore, its of note that women with history of depression prior to pregnancy or major depression during pregnancy are more likely to experience postpartum depression (27), and consequences of postpartum depression might be more severe for women, since it has shown to be associated with an increased risk of self-harm such as suicide (28,29). Therefore, because of possible severe maternal and fetal consequences and high risk of relapse, treatment of antepartum depression should be managed actively by a multi-professional team.

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Data sharing: No additional data available.

Contributor statement

All authors participated in designing the study. SR managed the dataset and performed statistical analyses. SML, HSN, MG, MRK and SH were statistical advisors. All authors contributed to the interpretation of the results, as well as to writing and editing the manuscript

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Table 1. Delivery characteristics and reproductive risk factors among women with singleton pregnancies with and without major depression during pregnancy and with and without a history of depression prior to pregnancy from 2002 to 2010 in Finland.

Characteristic	No major depression during pregnancy, *n*=493,037 (96.3%)	No major depression during pregnancy, *n*= 14,781 (2.9%)	Major depression during pregnancy, *n*=2,189 (0.4%)	Major depression during pregnancy, *n*=1,931 (0.4%)	*p value**
A history of depression prior to pregnancy	No	Yes	No	Yes	
Nulliparous % Multiparous	42.0 58.0	45.1 54.9	45.5 54.5	50.0 50.0	*≤0.001*
Mean maternal age, years (SD)	29.6 (5.4)	27.6 (6.0)	28.4 (6.2)	28.7 (6.6)	≤0.001
Mean gestational age, wk (SD)	39.8 (1.8)	39.7 (1.9)	39.4 (2.0)	39.5 (2.0)	≤0.001
Mode of delivery % Vaginal spontaneous Breech Forceps Vacuum assistance Caesarean section	 75.8 0.6 0.1 7.2 15.9	 74.8 0.6 0.1 7.5 17.1	 72.6 0.2 0.1 7.5 19.6	 70.4 0.4 0.0 7.7 21.5	≤0.001
Mean birth weight, g (SD)	3531.4 (550)	3479.0 (568)	3453.1 (580)	3456.3 (608)	≤0.001
Male fetal sex %	51.2	50.0	51.1	51.8	0.04
Major congenital anomalies %	4.0	5.2	5.6	5.9	≤0.001
Smoking status % Non-smoking Quit smoking during 1st trimester Smoking after 1st trimester Missing information	 83.2 3.7 10.5 2.6	 63.4 6.9 26.7 2.9	 66.1 6.5 25.1 2.3	 59.5 8.3 29.3 3.0	≤0.001
Married or living with a partner %	93.5	86.3	83.1	83.0	≤0.001
Socioeconomic status % Upper white-collar worker Lower white-collar worker Blue-collar worker Others [a] Missing information	 8.6 34.5 14.2 25.7 17.2	 3.7 25.8 16.0 31.0 23.6	 4.0 27.9 14.9 31.9 21.3	 3.8 25.5 15.3 30.0 25.3	≤0.001
Prior miscarriages %	20.7	23.6	23.3	23.2	≤0.001
Prior terminations %	12.2	22.4	19.8	21.7	≤0.001
In vitro fertilization (IVF) %	1.6	1.2	0.9	1.3	≤0.001
Anaemia, ≤100 g/L %	1.6	2.6	3.5	2.8	≤0.001
Placenta praevia %	0.3	0.2	0.2	0.4	0.54
Placental abruption %	0.3	0.4	0.5	0.7	0.07
Preeclampsia %	1.2	1.3	0.9	1.2	0.52
Gestational diabetes %	11.2	13.4	14.5	17.6	≤0.001
Pre-existing diabetes %	8.4	10.9	11.6	13.6	≤0.001
Prior caesarean section %	10.6	10.5	10.3	10.2	0.90
Fear of childbirth %	4.6	11.4	15.0	17.5	≤0.001

SD=standard deviation, *chi-square or Kruskal-Wallis test, [a] 'Others' comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases,

Table 2. Unadjusted and adjusted odds ratios (aOR) of major depression during pregnancy among women with singleton pregnancies from 2002-2010 in Finland using women with no major depression during pregnancy without and with a history of depression prior to pregnancy as a reference population (categories 1 and 2).

Characteristic	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)
A history of depression prior to pregnancy	29.43 (27.62-31.35)	22.36 (20.86-23.98)
Maternal age (years)		
≤19	3.14 (2.79-3.52)	1.58 (1.38-1.81)
20–29	1	1
30–39	0.86 (0.81-0.92)	1.19 (1.11-1.28)
≥40	1.41 (1.22-1.63)	1.65 (1.41-1.94)
Nulliparous women	1.25 (1.18-1.33)	1.21 (1.12-1.30)
Multiparous women	1	1
Smoking status		
Non-smoking	1	1
Quit smoking during 1st trimester	2.52 (2.23-2.84)	1.57 (1.38-1.80)
Smoking after 1st trimester	3.25 (3.03-3.49)	1.67 (1.53-1.81)
Missing information	1.32 (1.09-1.60)	1.09 (0.88-1.35)
Married/living with a partner	1	1
Single	2.86 (2.62-3.11)	1.63 (1.48-1.79)
Socioeconomic status		
Upper white-collar worker	1	1
Lower white-collar worker	1.69 (1.43-1.99)	1.42 (1.20-1.69)
Blue-collar worker	2.29 (1.93-2.73)	1.53 (1.27-1.84)
Others [a]	2.59 (2.20-3.05)	1.67 (1.40-1.98)
Missing information	2.88 (2.43-3.40)	1.66 (1.39-1.98)
Prior miscarriages	1.15 (1.07-1.24)	1.09 (1.00-1.18)
Prior terminations	1.82 (1.69-1.97)	1.14 (1.04-1.24)
In vitro fertilization (IVF)	0.70 (0.53-0.94)	0.78 (0.58-1.07)
Anaemia ≤100 g/L	2.02 (1.70-2.41)	1.49 (1.22-1.81)
Gestational diabetes	1.49 (1.37-1.62)	1.29 (1.11-1.50)
Pre-existing diabetes	1.56 (1.42-1.71)	1.10 (0.93-1.31)
Fear of childbirth	3.80 (3.49-4.13)	2.63 (2.39-2.89)
Male fetal sex	1.01 (0.95-1.07)	0.97 (0.91-1.04)

*ORs of major depression adjusted by history of depression prior to pregnancy, maternal age, parity, smoking status, marital status, SES, prior miscarriages, prior terminations, IVF, anaemia, gestational diabetes, pre-existing diabetes, fear of childbirth, and fetal sex.

[a] Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases, CI=confidence interval

Table 3. Unadjusted and adjusted odds ratios (OR) of major depression during pregnancy separately for women without (category 3) and with a history of depression prior to pregnancy (category 4) among women with singleton pregnancies from 2002-2010 in Finland using women without major depression without a history of depression prior to pregnancy (category 1) [a] and women without major depression without and with a history of depression prior to pregnancy (categories 1 and 2) [b] as reference groups.

Characteristic	Major depression during pregnancy without a history of depression prior to pregnancy [a]		Major depression during pregnancy with a history of depression prior to pregnancy [b]	
	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)
Maternal age (years)				
≤19	3.02 (2.57-3.56)	1.77 (1.46-2.13)	3.42 (2.90-4.03)	1.86 (1.55-2.24)
20–29	1	1	1	1
30–39	0.85 (0.77-0.93)	0.96 (0.87-1.06)	0.87 (0.79-0.96)	1.04 (0.93-1.15)
≥40	1.21 (0.98-1.49)	1.20 (0.96-1.50)	1.63 (1.34-1.99)	1.70 (1.37-2.10)
Nulliparous women	1.15 (1.06-1.26)	1.09 (0.99-1.20)	1.38 (1.26-1.51)	1.35 (1.22-1.50)
Multiparous women	1	1	1	1
Smoking status				
Non-smoking	1	1	1	1
Quit smoking during 1st trimester	2.19 (1.84-2.61)	1.75 (1.45-2.11)	3.03 (2.55-3.56)	2.51 (2.11-2.99)
Smoking after 1st trimester	3.02 (2.74-3.34)	2.25 (2.01-2.52)	3.72 (3.36-4.12)	2.83 (2.52-3.17)
Missing information	1.13 (0.85-1.49)	0.99 (0.72-1.34)	1.57 (1.20-2.05)	1.49 (1.12-1.98)
Married/living with a partner	1	1	1	1
Single	2.94 (2.62-3.30)	2.08 (1.84-2.35)	2.87 (2.53-3.24)	1.80 (1.58-2.05)
Socioeconomic status				
Upper white-collar worker	1	1	1	1
Lower white-collar worker	1.75 (1.39-2.19)	1.60 (1.26-2.01)	1.64 (1.28-2.09)	1.42 (1.11-1.83)
Blue-collar worker	2.27 (1.79-2.88)	1.72 (1.34-2.21)	2.37 (1.84-3.06)	1.66 (1.27-2.16)
Others [c]	2.68 (2.14-3.35)	2.17 (1.72-2.73)	2.56 (2.01-3.26)	1.94 (1.51-2.50)
Missing information	2.67 (2.13-3.36)	2.02 (1.59-2.57)	3.20 (2.51-4.09)	2.36 (1.83-3.04)
Prior miscarriages	1.16 (1.05-1.28)	1.20 (1.08-1.33)	1.15 (1.04-1.28)	1.17 (1.04-1.31)
Prior terminations	1.77 (1.59-1.97)	1.35 (1.20-1.51)	1.94 (1.74-2.16)	1.41 (1.25-1.58)
In vitro fertilization	0.57 (0.37-0.89)	0.71 (0.46-1.11)	0.85 (0.58-1.26)	0.93 (0.62-1.41)
Anaemia ≤100 g/L	2.28 (1.81-2.86)	2.03 (1.60-2.59)	1.79 (1.36-2.34)	1.41 (1.05-1.90)
Gestational diabetes	1.34 (1.19-1.51)	1.09 (0.88-1.36)	1.67 (1.49-1.88)	1.53 (1.24-1.88)
Pre-existing diabetes	1.44 (1.26-1.64)	1.33 (1.04-1.68)	1.71 (1.50-1.95)	1.18 (0.94-1.49)
Fear of childbirth	3.64 (3.23-4.09)	3.80 (3.36-4.29)	4.16 (3.70-4.68)	4.35 (3.85-4.92)
Male fetal sex	0.99 (0.91-1.08)	1.00 (0.92-1.09)	0.98 (0.89-1.07)	1.03 (0.94-1.13)

*ORs of major depression during pregnancy adjusted by maternal age, parity, smoking status, marital status, SES, prior miscarriages, prior terminations, IVF, anaemia, gestational diabetes, pre-existing diabetes, fear of childbirth, and fetal sex.

[c] Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases, CI=confidence interval

Table 4. Adjusted odds ratios (ORs) of major depression during pregnancy associated with adverse perinatal outcomes among singleton births in Finland from 2002-2010.

Perinatal outcome	**Model 1** adjusted by major depression during pregnancy	**Model 2** adjusted by Model 1 + age and parity	**Model 3**adjusted by Model 2 + socioeconomic status (SES)	**Model 4** adjusted by Model 2 + smoking	**Model 5** adjusted by Model 2 + SES and smoking
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Admission to a NICU	1.79 (1.65-1.95)	1.78 (1.64-1.94)	1.78 (1.64-1.93)	1.68 (1.55-1.83)	1.69 (1.55-1.84)
Stillbirth	1.97 (1.33-2.93)	2.01 (1.35-2.99)	1.86 (1.25-2.76)	1.88 (1.27-2.80)	1.77 (1.19-2.63)
Early neonatal death	1.08 (0.49-2.42)	1.13 (0.50-2.51)			
Preterm birth (<37 weeks)	1.57 (1.39-1.77)	1.57 (1.39-1.77)	1.55 (1.37-1.75)	1.49 (1.32-1.68)	1.48 (1.31-167)
LBW (<2500 grams)	1.56 (1.36-1.79)	1.55 (1.35-1.79)	1.53 (1.33-1.76)	1.37 (1.19-1.58)	1.36 (1.18-1.56)
SGA (<-2 SD below mean birth weight)	1.46 (1.27-1.67)	1.41 (1.23-1.62)	1.39 (1.21-1.59)	1.18 (1.03-1.36)	1.17 (1.02-1.35)
Apgar scores (<7 at 5 minute) [a]	2.13 (1.79-2.54)	2.11 (1.77-2.51)	2.07 (1.74-2.47)	2.05 (1.72-2.45)	2.02 (1.70-2.41)
Fetal venous pH <7.15 at birth [a, b]	1.37 (1.06-1.76)	1.32 (1.03-1.71)	1.33 (1.03-1.72)	1.35 (1.05-1.74)	1.36 (1.06-1.76)
Major congenital anomaly	1.47 (1.29-1.67)	1.48 (1.29-1.69)	1.47 (1.29-1.68)	1.44 (1.26-1.65)	1.44 (1.26-1.64)

[a] available since 2004, [b] gathered selectively by indication, NICU= neonatal intensive care unit, LBW= low birth weight, SGA= small for gestational age, CI=confidence interval, SD=standard deviation

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
D **Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **OK**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **OK**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **OK**
Objectives	3	State specific objectives, including any prespecified hypotheses **OK**
Methods		
Study design	4	Present key elements of study design early in the paper **OK**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **OK**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **OK**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **NA**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **OK**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **OK**
Bias	9	Describe any efforts to address potential sources of bias **OK**
Study size	10	Explain how the study size was arrived at **TOTAL POPULATION**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **OK**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **OK**
		(*b*) Describe any methods used to examine subgroups and interactions **OK**
		(*c*) Explain how missing data were addressed **OK**
		(*d*) If applicable, explain how loss to follow-up was addressed **NO**
		(*e*) Describe any sensitivity analyses **OK**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **OK**
		(b) Give reasons for non-participation at each stage **NO**
		(c) Consider use of a flow diagram **NA**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **OK**
		(b) Indicate number of participants with missing data for each variable of interest **OK**
		(c) Summarise follow-up time (eg, average and total amount) **OK**
Outcome data	15*	Report numbers of outcome events or summary measures over time **OK**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included **OK**
		(*b*) Report category boundaries when continuous variables were categorized OK
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **OK**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **OK**
Discussion		
Key results	18	Summarise key results with reference to study objectives **OK**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **OK**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **OK**
Generalisability	21	Discuss the generalisability (external validity) of the study results **OK**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **OK**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Risk factors for and perinatal outcomes of major depression during pregnancy – a population-based analysis during 2002-2010 in Finland

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Risk factors for and perinatal outcomes of major depression during pregnancy – a population-based analysis during 2002-2010 in Finland

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Abstract

Objectives: To identify risk factors for and the consequences (several adverse perinatal outcomes) of physician-diagnosed major depression during pregnancy treated in specialized healthcare.

Design: A population-based cross sectional study

Setting: Data were gathered from Finnish health registers for 1996-2010.

Participants: All singleton births (*n*=511,938) for 2002-2010 in Finland

Primary outcome measures: Prevalence, risk factors and consequences of major depression during pregnancy

Results: Among 511,938 women, 0.8% experienced major depression during pregnancy, of which 46.9% had a history of depression prior to pregnancy. After history of depression the second strongest associated factor for major depression was fear of childbirth, with a 2.6-fold (adjusted odds ratio (aOR=2.63, 95% confidence interval (CI)=2.39-2.89) increased prevalence. The risk profile of major depression also included adolescent or advanced maternal age, low or unspecified socioeconomic status (SES), single marital status, smoking, prior pregnancy terminations, anaemia and gestational diabetes regardless of a history of depression. Outcomes of pregnancies were worse among women with than without major depression. The contribution of smoking was substantial to modest for small for gestational age newborn (< -2 standard deviation below mean birth), low birth weight (< 2,500 g), preterm birth (<37 weeks) and admission to neonatal intensive care associated with major depression was, whereas SES made only a minor contribution.

Conclusions: Physician-diagnosed major depression during pregnancy was found to be rare. The strongest risk factor was history of depression prior to pregnancy. Other associated factors were fear of childbirth, low SES, lack of social support and unhealthy reproductive behavior such as

smoking. Outcomes of pregnancies were worse among women with than without major depression. Smoking during pregnancy made a substantial to modest contribution to adverse outcomes associated with depression during pregnancy.

Article summary

Article focus

- To identify risk factors for and the consequences of physician-diagnosed major depression during pregnancy defined according to the International Classification of Diseases (ICD) - 10 codes during pregnancy.

Key messages

- After history of depression prior to pregnancy the strongest associated factor for major depression during pregnancy was physician-diagnosed fear of childbirth.

- Outcomes of pregnancies were worse among women with than without major depression.

Strengths and limitations

- Strengths of this study were the population-based data gathered from three mandatory national health registers, and physician-diagnosed depression defined by ICD-10 codes.

- Possible limitations were that we did not have information on women diagnosed and treated for major depression during pregnancy in primary health care, information on history of depression was based on outpatient and inpatient visits only since 1998 and 1996, respectively, and we did not have information on antidepressant medication at an individual level.

Introduction

Depression is globally one of the leading causes of disease burden for women.(1) A previous large population-based study reported that 0.8% of 32.2 million women had physician-diagnosed depression at the time of delivery in United States (US) during 1998-2005.(2) A recent systematic review concluded that according to multivariable analyses, life stress, lack of social support and domestic violence were associated with an increased risk of depression during pregnancy, whereas maternal anxiety, history of depression, unintended pregnancy, lack of private medical insurance, low income, low education, smoking, single marital status and poor relationship were only significant predictors in bivariable analysis.(3) The authors of this review highlighted several limitations of previous studies, such as differences in the methods used to screen depression, study population, risk factors and confounders included in statistical analyses.

To date, only a few studies have evaluated the role of a history of depression as a predictor of antepartum depression, i.e., depression during pregnancy, but the association was not found to be statistically significant according to a multivariable analysis.(3) Further, several previous studies have shown that diabetes mellitus, gestational diabetes,(2,4) preeclampsia,(2,5) anaemia, caesarean section and placental abnormalities(2) are more prevalent among women suffering from perinatal depression.

Antepartum and postpartum depression represent a risk for children's short- and long-term wellbeing.(6) Several studies have reported an association between antepartum depression and risk of preterm birth, but no association with other adverse outcomes, such as low birth weight, admission to a neonatal intensive care unit, preeclampsia and low Apgar scores, as shown in a systematic review and meta-analysis.(7) However, many of these studies were potentially underpowered because of small sample sizes and were also heterogeneous with respect to the study population and analyses. Further, the use of different methods to measure and define depression

raises questions about whether all studies really measured clinically diagnosed major depression.(7) Further, the previous mentioned large population-based study from US found that physician-diagnosed depression at the time of birth was associated with an increased prevalence of preterm birth, fetal growth restriction, fetal abnormalities, fetal distress and fetal death.(2)

The aim of the present large population based cross sectional study was to identify risk factors for major depression during pregnancy based on ICD-10 codes (International Classification of Diseases) treated in specialized healthcare units, especially an association between a prior history of depression and antepartum depression that was only studied by few smaller studies.(3) Furthermore, we studied whether major depression during pregnancy was associated with adverse perinatal outcomes and the degree to which this association was attenuated or mediated by women's SES and smoking (strongly associated with adverse perinatal outcomes)(8) during pregnancy in Finland. Most previous studies considering an association between adverse perinatal outcomes and depression were small and population based studies were scarce.(7) Further, differences in health care services such as access to antenatal care might limit generalizability of the large previous study from US.(2) In Finland, with around 5.5 million residents, health care services are mainly publicly funded and all women have free access to antenatal care.

Materials and Methods

Data and population

Data were gathered from three national health registers currently maintained by the National Institute for Health and Welfare and were linked using women's encrypted unique personal identification numbers. The Finnish MBR contains demographics, pregnancy and delivery characteristics and diagnoses on all live births or stillbirths delivered after the 22nd gestational week or weighing 500 g or more during the first postnatal week recorded since 1987. The MBR

data was supplemented by information on maternal health (major depression, preeclampsia, gestational diabetes, pre-existing diabetes, and fear of childbirth) gathered and defined based on ICD-10 codes from the Hospital Discharge Register (HDR). The HDR was established in 1969 and contains information on all aspects of inpatient care and outpatient visits in Finnish hospitals. Information on major congenital anomalies (yes or no) was gathered and the Register of Congenital Malformations established 1963. Data included all women with singleton births (*n*=511,938) from 2002-2010; multiple births (*n*=15,767) were excluded because they carry a higher risk of complications. The present time period was chosen since information on depression (i.e., a history of depression prior to pregnancy) was available since 1996 for inpatient visits and since 1998 for outpatient visits.

The National Institute for Health and Welfare approved study plan and use of the data for the study as required by the national data protection legislation in Finland (Reference number 1749/5.05.00/2011).

Variables and definitions

Depression, physician-diagnosed, was defined by ICD-10 codes F31.3, F31.5 and F32-34 and women were grouped into four categories; 1) no major depression during pregnancy, and no history of depression prior to pregnancy, 2) no major depression during pregnancy with a history of depression prior to pregnancy, 3) major depression during pregnancy with no history of depression prior to pregnancy, and 4) major depression during pregnancy with a history of depression prior to pregnancy. Information on major depression was based on outpatient visits (patients without overnight hospitalization) in specialized health care since 1998 and inpatient visits (at least an overnight stay at a hospital) specialized health care since 1996 gathered from the HDR. In Finland, general practitioners and midwives in health care centers provide primary health care such as antenatal care, and specialists in regional and university teaching hospitals provide specialized

health care. Health care professionals at both levels are instructed to evaluate the mother's mental wellbeing as part of all appointments. Parity was categorized as either nulliparous, if women had no prior births, or multiparous, if women had at least one prior birth. The gestational age was estimated based on first- or second-trimester ultrasonography measurements. Mode of delivery was classified as vaginal spontaneous, breech, forceps, vacuum assisted or caesarean section (CS). Smoking habits during pregnancy based on self-reported information was grouped into three categories: non-smoking, quitted smoking during the first trimester, and continued smoking after the first trimester, i.e., smoking. Marital status was classified as either married (including women living with a partner) or single. SES was grouped into five categories based on the Finnish Classification of Occupations(9) which was developed according to international recommendations: upper white-collar workers, such as physicians and lawyers; lower white-collar workers, such as nurses and secretaries; blue-collar workers, such as cooks and cashiers; others; and missing information, as categorized and published elsewhere(10) 'Others' comprised 25.9% (*n*=132,391) of all cases and included all births with unspecified occupations, such as entrepreneurs, students, retired, unemployed and housewives. The category with missing SES information comprised 17.4% (*n*=89,041) of all births. Information on prior CS, induction, miscarriages and pregnancy terminations was dichotomous (yes or no). Information on in vitro fertilization (IVF) included intracytoplasmic sperm injection and frozen embryo transfers. Anaemia was defined as hemoglobin levels ≤100 g/L. Placenta praevia (O44), placental abruption (O45), preeclampsia (O14 and O15), gestational diabetes (O24.4), and maternal preexisting diabetes (O24.0 and O24.1) were gathered from the HDR based on ICD-10 codes. Fear of childbirth was defined by national ICD-10 code O99.80. Feelings towards childbirth are asked all women in antenatal care and women experiencing significant fear of childbirth that cannot be counseled during antenatal visits in primary health care or making CS request due to fear of childbirth are referred to specialist maternity care as described previously.(11,12)

Adverse perinatal outcomes: Admission to a neonatal intensive care unit (NICU) was defined as at least 24 hour surveillance at neonatal intensive care. Stillbirth was defined as fetal death from 22 gestational weeks onwards or birth weight 500 grams or more and early neonatal death as death during the first seven postnatal days. Preterm birth was defined as gestational age < 37+0 weeks. Low birth weight (LBW) was defined as a birth weight of less than 2,500 grams. Small for gestational age (SGA) was defined as a sex- and parity-specific birth weight more than two standard deviation (SD) below the mean weight for gestational based on the national 2013 population-based reference.(13) Five minute Apgar scores < 7 and infant's vein pH < 7.15 were considered low (taken by indication and both available since 2004).

Statistical analyses

Differences between the four categories of women defined by their depression history as described previously were evaluated by chi-square test for dichotomous or categorical variables and Kruskal-Wallis test for continuous variables. Unadjusted and adjusted odds ratios (ORs) of major depression were determined by using logistic regression analyses. The outcome event of interest was major depression during pregnancy (categories 3 and 4), and the reference group was all women without major depression without or with a history of depression prior to pregnancy (categories 1 and 2). All covariates were determined based on literature and results of bivariable analyses.

To address the second research aim regarding the contribution of major depression to adverse perinatal outcomes with or without further control for smoking, SES and other covariates, a second set of logistic models was fitted. For each perinatal outcome, a preliminary model (Model 1) was used to estimate the association between major depression and perinatal outcome. Then, additional covariates were added in subsequent models: adjustment for age and parity (Model 2), adjustment for Model 2 variables plus SES (Model 3), adjustment for Model 2 variables plus smoking (Model 4), and adjustment for all variables simultaneously (Model 5). Furthermore, multiple imputations

were performed to study whether missing information on SES affected our results of logistic regression analysis. The data were analyzed using SPSS for Windows 19.0, Chicago, IL. Differences were deemed to be significant if $p < 0.05$. In addition, 95% confidence intervals (CIs) were calculated.

Results

In total, 0.8% (*n*=4,120) of 511,938 women with singleton pregnancy suffered from major depression during pregnancy as diagnosed by ICD-10 codes in specialized healthcare units. Of all the women with major depression during pregnancy, 53.1% (2,189 of 4,120) did not have a history of depression prior to pregnancy. Table 1 shows demographics, delivery characteristics and reproductive factors for women with and without major depression during pregnancy according to their history of depression prior to pregnancy. Women who suffered from major depression during pregnancy were more frequently nulliparous, younger, and gave birth by caesarean section, to a male infant, and had a lower mean birth weight compared with women with no depression during pregnancy. Further, they more frequently were smokers, of unspecified SES and had reproductive risk factors, such as prior pregnancy terminations, anaemia, major congenital anomalies, gestational diabetes and maternal pre-existing diabetes, and suffered more frequently from fear of childbirth compared with women with no major depression during pregnancy.

Table 2 shows risk factors for major depression during pregnancy (categories 3 and 4) using women with no major depression without or with a history of depression prior to pregnancy (categories 1 and 2) as a reference population. The strongest risk/associated factors for major depression during pregnancy were a history of depression prior to pregnancy and fear of childbirth, which were associated with a 22.4- and 2.6-fold increased prevalence of major depression during pregnancy, respectively. An increased prevalence of major depression during pregnancy was also associated with adolescent and advanced maternal age, smoking during pregnancy, single marital status, prior

pregnancy terminations of pregnancy, low or unspecified SES, anaemia and gestational diabetes. We performed all the analyses using multiple imputed data, but the results did not change (data not shown).

Pregnancies of women who suffered from major depression during pregnancy more frequently resulted in adverse perinatal outcomes, such as, stillbirth, preterm birth, LBW, SGA, Apgar scores < 7 at 5 minute, fetal venous pH < 7.15 at birth, admission to a neonatal intensive care unit and major congenital anomalies, compared with women without major depression during pregnancy (Table 3). Major depression was not associated with early neonatal death. Smoking appeared to contribute the most to the increased prevalence of SGA, LBW, preterm birth, stillbirth and admission to a neonatal intensive care associated with major depression, but made only a minor contribution to the increased prevalence of other perinatal outcomes, except early neonatal death and low fetal venous pH, associated with major depression during pregnancy. SES made a minor contribution to the increased prevalence of all perinatal outcomes, except admission to a neonatal unit, early neonatal death and low fetal venous pH, associated with major depression during pregnancy.

Discussion

Main findings

The prevalence of major depression during pregnancy among women with singleton births was 0.8%, which is consistent with a previous population- and diagnosis-based study,(2) but substantially lower than 3.1-12.8% reported by smaller studies utilizing mostly self-reported screening or interviews.(14-16) More than half of the episodes occurred in women without a history of depression prior to pregnancy. The second strongest associated factor for major depression

during pregnancy after history of depression was fear of childbirth, which was associated with three-fold increased odds of major depression during pregnancy. Major depression during pregnancy occurred most frequently in women with low or unspecified SES, single marital status and unhealthy behavior, such as smoking. Outcomes of pregnancies were substantially worse than in women with no major depression during pregnancy. Smoking during pregnancy contributed substantially to an increased prevalence of SGA, LBW, preterm birth and admission to a neonatal unit associated with major depression during pregnancy.

Strengths and limitations

The present study has several strengths: the data included the entire childbearing population gathered from three national health registers with high-quality data (17,18) depression during pregnancy was diagnosed by a physician, and some novel risk factors, such as fear of childbirth, were studied. However, we acknowledge several limitations with the present study. Information on depression covered only cases diagnosed and treated in specialized medical care units. We did not have information on women experienced major depression during pregnancy diagnosed treated in primary health care. However, it is likely that most high-risk pregnancies such as women with diagnosed depression were treated in by specialized maternity care, thus providing us information on most women with major depression. Further, information on depression was available only since 1996 for inpatient visits and since 1998 for outpatient visits, and therefore we may not have had complete information on all pre-pregnancy depression episodes. In addition, we had no information on antidepressant medication at an individual level and history of adverse pregnancy outcomes, and thus could not assess their roles as confounders in the multivariable analyses. Further, information on SES could not be defined or was missing for approximately 40% of the births. SES is self-reported and optional, and due to confidentiality concerns, some women chose not provide it. However, the socio-demographics of this group were close to those of the general population, and

multiple data imputations of missing information did not change the results (data not shown). Further, SES was solely defined based on maternal occupation at birth that is related to education and income in Finland, and is an appropriate available indicator for studies on socioeconomic health disparity.(19,20) Further, due to data protection issues we did not have information on spouses' SES. No adjustment was made for multiple comparisons, and model results should be interpreted accordingly.

Interpretation

History of depression prior to pregnancy was the strongest predisposing factor for major depression during pregnancy. However, more than half of the women with major depression during pregnancy had no history of depression indicating that the first episode of depression is not uncommon during pregnancy. A previous systematic review(3) did not report a positive association between a history of depression prior to pregnancy and antenatal depression, but there were only three studies with multivariable analyses. The three previous studies were with small sample size and had heterogeneity in assessment for a prior history of depression.(3) A novel finding of the present study was that physician-diagnosed fear of childbirth was associated with on the order of three-fold increased prevalence of major depression during pregnancy. Several previous studies reported an association between anxiety disorders and major depression during pregnancy as previously reviewed.(3) We showed also that low SES, lack of social support, and unhealthy reproductive behavior, such as smoking, were risk factors for major depression during pregnancy. These results are partly in line with a previous systematic review suggesting that smoking, anxiety symptoms, lower SES, life stress, and lack of social support were associated with an increased prevalence of antepartum depression.(3) Further, the association between gestational diabetes and maternal pre-existing diabetes was in accordance with the results of previous studies.(2,4) However, our results did not confirm the association between preeclampsia and perinatal depression found in previous

studies.(2,5) In general, it has been suggested that depression and other pregnancy morbidities, such as diabetes and preeclampsia, would have a partially common physiological pathway.(21) Risk factors for major depression during pregnancy did not vary substantially between women with and without a history of depression (data not shown).

Our results showed that outcomes of pregnancies affected by major depression during pregnancy were worse than pregnancies not affected by major depression during pregnancy. Several previous studies reviewed found a positive association between preterm birth and depression during pregnancy, but not with other outcomes such as LBW, Apgar scores and admission to NICU.(7) However, the authors suggest that the results might be affected by differences in definition of perinatal outcomes (many studies did not use standard definitions), and that many studies were underpowered or did not have all important covariates such as maternal smoking.(7)

Adverse perinatal outcomes are strongly associated with SES and health behavior such as smoking.(8) In the present study it seemed that smoking mediated the association between adverse perinatal outcomes and depression during pregnancy. Based on previous systematic reviews and meta-analysis, antidepressant medication during pregnancy has been shown to be associated with preterm birth,(22) lower Apgar scores,(22) and poor neonatal adaptation,(23) but not with major congenital anomalies.(24) Further, exposure specifically to SSRIs has been shown to be associated with preterm birth,(25) and low Apgar scores,(26) but not with stillbirth, neonatal mortality or postnatal mortality.(27) A limitation in the present study was that we could not assess the contribution of antidepressant medication to adverse perinatal outcomes associated with depression during pregnancy, since we did not have access to this information on an individual level. Among the total delivering population, the use of selective serotonin reuptake inhibitors (SSRIs) ranged from 0.5% in 1997 to 3.7% in 2010 in Finland.

Conclusions

Using a large nine-year national population-based data on all singleton births, we concluded that physician-diagnosed episodes of major depression in specialized healthcare units during pregnancy were rare. The strongest risk factor for major depression was history of depression prior to pregnancy. This result may help clinicians to recognize the risk of depression. Other risk factors for major depression during pregnancy were low SES, lack of social support and unhealthy behavior during pregnancy, such as smoking. Major depression was also associated with fear of childbirth. Outcomes of pregnancies among women affected by major depression during pregnancy were worse than in unaffected women, but smoking during pregnancy made a substantial or modest contribution to the increased prevalence of SGA, LBW, preterm and admission to a neonatal unit associated with depression during pregnancy. Furthermore, its of note that women with history of depression prior to pregnancy or major depression during pregnancy are more likely to experience postpartum depression,(28,29) and consequences of postpartum depression might be more severe for women, since it has shown to be associated with an increased risk of self-harm such as suicide.(30,31) Therefore, because of possible severe maternal and fetal consequences and high risk of relapse, treatment of antepartum depression should be managed actively by a multi-professional team.

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Contributor statement

All authors participated in designing the study. SR managed the dataset and performed statistical analyses. SML, HSN, MG, MRK and SH were statistical advisors. All authors contributed to the interpretation of the results, as well as to writing and editing the manuscript.

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Table 1. Delivery characteristics and reproductive risk factors among women with singleton pregnancies with and without major depression during pregnancy and with and without a history of depression prior to pregnancy from 2002 to 2010 in Finland.

Characteristic	No major depression during pregnancy, *n*=493,037 (96.3%)	No major depression during pregnancy, *n*= 14,781 (2.9%)	Major depression during pregnancy, *n*=2,189 (0.4%)	Major depression during pregnancy, *n*=1,931 (0.4%)	*p value**
A history of depression prior to pregnancy	No	Yes	No	Yes	
Nulliparous % Multiparous	42.0 58.0	45.1 54.9	45.5 54.5	50.0 50.0	*≤0.001*
Mean maternal age, years (SD)	29.6 (5.4)	27.6 (6.0)	28.4 (6.2)	28.7 (6.6)	≤0.001
Mean gestational age, wk (SD)	39.8 (1.8)	39.7 (1.9)	39.4 (2.0)	39.5 (2.0)	≤0.001
Mode of delivery % Vaginal spontaneous Breech Forceps Vacuum assistance Caesarean section	 75.8 0.6 0.1 7.2 15.9	 74.8 0.6 0.1 7.5 17.1	 72.6 0.2 0.1 7.5 19.6	 70.4 0.4 0.0 7.7 21.5	≤0.001
Mean birth weight, g (SD)	3531.4 (550)	3479.0 (568)	3453.1 (580)	3456.3 (608)	≤0.001
Male fetal sex %	51.2	50.0	51.1	51.8	0.04
Major congenital anomalies %	4.0	5.2	5.6	5.9	≤0.001
Smoking status % Non-smoking Quit smoking during 1st trimester Smoking after 1st trimester Missing information	 83.2 3.7 10.5 2.6	 63.4 6.9 26.7 2.9	 66.1 6.5 25.1 2.3	 59.5 8.3 29.3 3.0	≤0.001
Married or living with a partner %	93.5	86.3	83.1	83.0	≤0.001
Socioeconomic status % Upper white-collar worker Lower white-collar worker Blue-collar worker Others [a] Missing information	 8.6 34.5 14.2 25.7 17.2	 3.7 25.8 16.0 31.0 23.6	 4.0 27.9 14.9 31.9 21.3	 3.8 25.5 15.3 30.0 25.3	≤0.001
Prior miscarriages %	20.7	23.6	23.3	23.2	≤0.001
Prior terminations %	12.2	22.4	19.8	21.7	≤0.001
In vitro fertilization (IVF) %	1.6	1.2	0.9	1.3	≤0.001
Anaemia, ≤100 g/L %	1.6	2.6	3.5	2.8	≤0.001
Placenta praevia %	0.3	0.2	0.2	0.4	0.54

Placental abruption %	0.3	0.4	0.5	0.7	0.07
Preeclampsia %	1.2	1.3	0.9	1.2	0.52
Gestational diabetes %	11.2	13.4	14.5	17.6	≤0.001
Pre-existing diabetes %	8.4	10.9	11.6	13.6	≤0.001
Prior caesarean section %	10.6	10.5	10.3	10.2	0.90
Fear of childbirth %	4.6	11.4	15.0	17.5	≤0.001

SD=standard deviation, *chi-square or Kruskal-Wallis test, [a] 'Others' comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases,

Table 2. Unadjusted and adjusted odds ratios (aOR) of major depression during pregnancy among women with singleton pregnancies from 2002-2010 in Finland using women with no major depression during pregnancy without and with a history of depression prior to pregnancy as a reference population (categories 1 and 2).

Characteristic	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)
A history of depression prior to pregnancy	29.43 (27.62-31.35)	22.36 (20.86-23.98)
Maternal age (years)		
≤19	3.14 (2.79-3.52)	1.58 (1.38-1.81)
20–29	1	1
30–39	0.86 (0.81-0.92)	1.19 (1.11-1.28)
≥40	1.41 (1.22-1.63)	1.65 (1.41-1.94)
Nulliparous women	1.25 (1.18-1.33)	1.21 (1.12-1.30)
Multiparous women	1	1
Smoking status		
Non-smoking	1	1
Quit smoking during 1st trimester	2.52 (2.23-2.84)	1.57 (1.38-1.80)
Smoking after 1st trimester	3.25 (3.03-3.49)	1.67 (1.53-1.81)
Missing information	1.32 (1.09-1.60)	1.09 (0.88-1.35)
Married/living with a partner	1	1
Single	2.86 (2.62-3.11)	1.63 (1.48-1.79)
Socioeconomic status		
Upper white-collar worker	1	1
Lower white-collar worker	1.69 (1.43-1.99)	1.42 (1.20-1.69)
Blue-collar worker	2.29 (1.93-2.73)	1.53 (1.27-1.84)
Others [a]	2.59 (2.20-3.05)	1.67 (1.40-1.98)
Missing information	2.88 (2.43-3.40)	1.66 (1.39-1.98)
Prior miscarriages	1.15 (1.07-1.24)	1.09 (1.00-1.18)
Prior terminations	1.82 (1.69-1.97)	1.14 (1.04-1.24)
In vitro fertilization (IVF)	0.70 (0.53-0.94)	0.78 (0.58-1.07)
Anaemia ≤100 g/L	2.02 (1.70-2.41)	1.49 (1.22-1.81)
Gestational diabetes	1.49 (1.37-1.62)	1.29 (1.11-1.50)
Pre-existing diabetes	1.56 (1.42-1.71)	1.10 (0.93-1.31)
Fear of childbirth	3.80 (3.49-4.13)	2.63 (2.39-2.89)
Male fetal sex	1.01 (0.95-1.07)	0.97 (0.91-1.04)

*ORs of major depression adjusted by history of depression prior to pregnancy, maternal age, parity, smoking status, marital status, SES, prior miscarriages, prior terminations, IVF, anaemia, gestational diabetes, pre-existing diabetes, fear of childbirth, and fetal sex.

[a] Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases, CI=confidence interval

Table 3. Adjusted odds ratios (ORs) of major depression during pregnancy associated with adverse perinatal outcomes among singleton births in Finland from 2002-2010.

Perinatal outcome	**Model 1** adjusted by major depression during pregnancy	**Model 2** adjusted by Model 1 + age and parity	**Model 3** adjusted by Model 2 + socioeconomic status (SES)	**Model 4** adjusted by Model 2 + smoking	**Model 5** adjusted by Model 2 + SES and smoking
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Admission to a NICU	1.79 (1.65-1.95)	1.78 (1.64-1.94)	1.78 (1.64-1.93)	1.68 (1.55-1.83)	1.69 (1.55-1.84)
Stillbirth	1.97 (1.33-2.93)	2.01 (1.35-2.99)	1.86 (1.25-2.76)	1.88 (1.27-2.80)	1.77 (1.19-2.63)
Early neonatal death	1.08 (0.49-2.42)	1.13 (0.50-2.51)			
Preterm birth (<37 weeks)	1.57 (1.39-1.77)	1.57 (1.39-1.77)	1.55 (1.37-1.75)	1.49 (1.32-1.68)	1.48 (1.31-167)
LBW (<2500 grams)	1.56 (1.36-1.79)	1.55 (1.35-1.79)	1.53 (1.33-1.76)	1.37 (1.19-1.58)	1.36 (1.18-1.56)
SGA (<-2 SD below mean birth weight)	1.46 (1.27-1.67)	1.41 (1.23-1.62)	1.39 (1.21-1.59)	1.18 (1.03-1.36)	1.17 (1.02-1.35)
Apgar scores (<7 at 5 minute) [a]	2.13 (1.79-2.54)	2.11 (1.77-2.51)	2.07 (1.74-2.47)	2.05 (1.72-2.45)	2.02 (1.70-2.41)
Fetal venous pH <7.15 at birth [a, b]	1.37 (1.06-1.76)	1.32 (1.03-1.71)	1.33 (1.03-1.72)	1.35 (1.05-1.74)	1.36 (1.06-1.76)
Major congenital anomaly	1.47 (1.29-1.67)	1.48 (1.29-1.69)	1.47 (1.29-1.68)	1.44 (1.26-1.65)	1.44 (1.26-1.64)

[a] available since 2004, [b] gathered selectively by indication, NICU= neonatal intensive care unit, LBW= low birth weight, SGA= small for gestational age, CI=confidence interval

Risk factors for and perinatal outcomes of major depression during pregnancy – a population-based analysis during 2002-2010 in Finland

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Abstract

Objectives: To identify risk factors for and the consequences (several adverse perinatal outcomes) of physician-diagnosed major depression during pregnancy treated in specialized healthcare.

Design: A population-based cross sectional study

Setting: Data were gathered from Finnish health registers for 1996-2010.

Participants: All singleton births (*n*=511,938) for 2002-2010 in Finland

Primary outcome measures: Prevalence, risk factors and consequences of major depression during pregnancy

Results: Among 511,938 women, 0.8% experienced major depression during pregnancy, of which 46.9% had a history of depression prior to pregnancy. After history of depression the second strongest associated factor for major depression was fear of childbirth, with a 2.6-fold (adjusted odds ratio (aOR=2.63, 95% confidence interval (CI)=2.39-2.89) increased prevalence. The risk profile of major depression also included adolescent or advanced maternal age, low or unspecified socioeconomic status (SES), single marital status, smoking, prior pregnancy terminations, anaemia and gestational diabetes regardless of a history of depression. Outcomes of pregnancies were worse among women with than without major depression. The contribution of smoking was substantial to modest for small for gestational age newborn (< -2 standard deviation below mean birth), low birth weight (< 2,500 g), preterm birth (<37 weeks) and admission to neonatal intensive care associated with major depression was, whereas SES made only a minor contribution.

Conclusions: Physician-diagnosed major depression during pregnancy was found to be rare. The strongest risk factor was history of depression prior to pregnancy. Other associated factors were fear of childbirth, low SES, lack of social support and unhealthy reproductive behavior such as

smoking. Outcomes of pregnancies were worse among women with than without major depression. Smoking during pregnancy made a substantial to modest contribution to adverse outcomes associated with depression during pregnancy.

Key words: Childbirth, Population Register, Depression, Register, Socioeconomic Status

Article summary

Article focus

- To identify risk factors for and the consequences of physician-diagnosed major depression during pregnancy defined according to the International Classification of Diseases (ICD) - 10 codes during pregnancy.

Key messages

- After history of depression prior to pregnancy the strongest associated factor for major depression during pregnancy was physician-diagnosed fear of childbirth.

- Outcomes of pregnancies were worse among women with than without major depression.

Strengths and limitations

- Strengths of this study were the population-based data gathered from three mandatory national health registers, and physician-diagnosed depression defined by ICD-10 codes.

- Possible limitations were that we did not have information on women diagnosed and treated for major depression during pregnancy in primary health care, information on history of depression was based on outpatient and inpatient visits only since 1998 and 1996, respectively, and we did not have information on antidepressant medication at an individual level.

Introduction

Depression is globally one of the leading causes of disease burden for women.(1) A previous large population-based study reported that 0.8% of 32.2 million women had physician-diagnosed depression at the time of delivery in United States (US) during 1998-2005.(2) A recent systematic review concluded that according to multivariable analyses, life stress, lack of social support and domestic violence were associated with an increased risk of depression during pregnancy, whereas maternal anxiety, history of depression, unintended pregnancy, lack of private medical insurance, low income, low education, smoking, single marital status and poor relationship were only significant predictors in bivariable analysis.(3) The authors of this review highlighted several limitations of previous studies, such as differences in the methods used to screen depression, study population, risk factors and confounders included in statistical analyses.

To date, only a few studies have evaluated the role of a history of depression as a predictor of antepartum depression, i.e., depression during pregnancy, but the association was not found to be statistically significant according to a multivariable analysis.(3) Further, several previous studies have shown that diabetes mellitus, gestational diabetes,(2,4) preeclampsia,(2,5) anaemia, caesarean section and placental abnormalities(2) are more prevalent among women suffering from perinatal depression.

Antepartum and postpartum depression represent a risk for children's short- and long-term wellbeing.(6) Several studies have reported an association between antepartum depression and risk of preterm birth, but no association with other adverse outcomes, such as low birth weight, admission to a neonatal intensive care unit, preeclampsia and low Apgar scores, as shown in a systematic review and meta-analysis.(7) However, many of these studies were potentially underpowered because of small sample sizes and were also heterogeneous with respect to the study population and analyses. Further, the use of different methods to measure and define depression

raises questions about whether all studies really measured clinically diagnosed major depression.(7) Further, the previous mentioned large population-based study from US found that physician-diagnosed depression at the time of birth was associated with an increased prevalence of preterm birth, fetal growth restriction, fetal abnormalities, fetal distress and fetal death.(2)

The aim of the present large population based cross sectional study was to identify risk factors for major depression during pregnancy based on ICD-10 codes (International Classification of Diseases) treated in specialized healthcare units, especially an association between a prior history of depression and antepartum depression that was only studied by few smaller studies.(3) Furthermore, we studied whether major depression during pregnancy was associated with adverse perinatal outcomes and the degree to which this association was attenuated or mediated by women's SES and smoking (strongly associated with adverse perinatal outcomes)(8) during pregnancy in Finland. Most previous studies considering an association between adverse perinatal outcomes and depression were small and population based studies were scarce.(7) Further, differences in health care services such as access to antenatal care might limit generalizability of the large previous study from US.(2) In Finland, with around 5.5 million residents, health care services are mainly publicly funded and all women have free access to antenatal care.

Materials and Methods

Data and population

Data were gathered from three national health registers currently maintained by the National Institute for Health and Welfare and were linked using women's encrypted unique personal identification numbers. The Finnish MBR contains demographics, pregnancy and delivery characteristics and diagnoses on all live births or stillbirths delivered after the 22nd gestational week or weighing 500 g or more during the first postnatal week recorded since 1987. The MBR

data was supplemented by information on maternal health (major depression, preeclampsia, gestational diabetes, pre-existing diabetes, and fear of childbirth) gathered and defined based on ICD-10 codes from the Hospital Discharge Register (HDR). The HDR was established in 1969 and contains information on all aspects of inpatient care and outpatient visits in Finnish hospitals. Information on major congenital anomalies (yes or no) was gathered and the Register of Congenital Malformations established 1963. Data included all women with singleton births (*n*=511,938) from 2002-2010; multiple births (*n*=15,767) were excluded because they carry a higher risk of complications. The present time period was chosen since information on depression (i.e., a history of depression prior to pregnancy) was available since 1996 for inpatient visits and since 1998 for outpatient visits.

The National Institute for Health and Welfare approved study plan and use of the data for the study as required by the national data protection legislation in Finland (Reference number 1749/5.05.00/2011).

Variables and definitions

Depression, physician-diagnosed, was defined by ICD-10 codes F31.3, F31.5 and F32-34 and women were grouped into four categories; 1) no major depression during pregnancy, and no history of depression prior to pregnancy, 2) no major depression during pregnancy with a history of depression prior to pregnancy, 3) major depression during pregnancy with no history of depression prior to pregnancy, and 4) major depression during pregnancy with a history of depression prior to pregnancy. Information on major depression was based on outpatient visits (patients without overnight hospitalization) in specialized health care since 1998 and inpatient visits (at least an overnight stay at a hospital) specialized health care since 1996 gathered from the HDR. In Finland, general practitioners and midwives in health care centers provide primary health care such as antenatal care, and specialists in regional and university teaching hospitals provide specialized

health care. Health care professionals at both levels are instructed to evaluate the mother's mental wellbeing as part of all appointments. Parity was categorized as either nulliparous, if women had no prior births, or multiparous, if women had at least one prior birth. The gestational age was estimated based on first- or second-trimester ultrasonography measurements. Mode of delivery was classified as vaginal spontaneous, breech, forceps, vacuum assisted or caesarean section (CS). Smoking habits during pregnancy based on self-reported information was grouped into three categories: non-smoking, quitted smoking during the first trimester, and continued smoking after the first trimester, i.e., smoking. Marital status was classified as either married (including women living with a partner) or single. SES was grouped into five categories based on the Finnish Classification of Occupations(9) which was developed according to international recommendations: upper white-collar workers, such as physicians and lawyers; lower white-collar workers, such as nurses and secretaries; blue-collar workers, such as cooks and cashiers; others; and missing information, as categorized and published elsewhere(10) 'Others' comprised 25.9% (*n*=132,391) of all cases and included all births with unspecified occupations, such as entrepreneurs, students, retired, unemployed and housewives. The category with missing SES information comprised 17.4% (*n*=89,041) of all births. Information on prior CS, induction, miscarriages and pregnancy terminations was dichotomous (yes or no). Information on in vitro fertilization (IVF) included intracytoplasmic sperm injection and frozen embryo transfers. Anaemia was defined as hemoglobin levels ≤100 g/L. Placenta praevia (O44), placental abruption (O45), preeclampsia (O14 and O15), gestational diabetes (O24.4), and maternal preexisting diabetes (O24.0 and O24.1) were gathered from the HDR based on ICD-10 codes. Fear of childbirth was defined by national ICD-10 code O99.80. Feelings towards childbirth are asked all women in antenatal care and women experiencing significant fear of childbirth that cannot be counseled during antenatal visits in primary health care or making CS request due to fear of childbirth are referred to specialist maternity care as described previously.(11,12)

Adverse perinatal outcomes: Admission to a neonatal intensive care unit (NICU) was defined as at least 24 hour surveillance at neonatal intensive care. Stillbirth was defined as fetal death from 22 gestational weeks onwards or birth weight 500 grams or more and early neonatal death as death during the first seven postnatal days. Preterm birth was defined as gestational age < 37+0 weeks. Low birth weight (LBW) was defined as a birth weight of less than 2,500 grams. Small for gestational age (SGA) was defined as a sex- and parity-specific birth weight more than two standard deviation (SD) below the mean weight for gestational based on the national 2013 population-based reference.(13) Five minute Apgar scores < 7 and infant's vein pH < 7.15 were considered low (taken by indication and both available since 2004).

Statistical analyses

Differences between the four categories of women defined by their depression history as described previously were evaluated by chi-square test for dichotomous or categorical variables and Kruskal-Wallis test for continuous variables. Unadjusted and adjusted odds ratios (ORs) of major depression were determined by using logistic regression analyses. The outcome event of interest was major depression during pregnancy (categories 3 and 4), and the reference group was all women without major depression without or with a history of depression prior to pregnancy (categories 1 and 2). All covariates were determined based on literature and results of bivariable analyses.

To address the second research aim regarding the contribution of major depression to adverse perinatal outcomes with or without further control for smoking, SES and other covariates, a second set of logistic models was fitted. For each perinatal outcome, a preliminary model (Model 1) was used to estimate the association between major depression and perinatal outcome. Then, additional covariates were added in subsequent models: adjustment for age and parity (Model 2), adjustment for Model 2 variables plus SES (Model 3), adjustment for Model 2 variables plus smoking (Model 4), and adjustment for all variables simultaneously (Model 5). Furthermore, multiple imputations

were performed to study whether missing information on SES affected our results of logistic regression analysis. The data were analyzed using SPSS for Windows 19.0, Chicago, IL. Differences were deemed to be significant if $p < 0.05$. In addition, 95% confidence intervals (CIs) were calculated.

Results

In total, 0.8% (*n*=4,120) of 511,938 women with singleton pregnancy suffered from major depression during pregnancy as diagnosed by ICD-10 codes in specialized healthcare units. Of all the women with major depression during pregnancy, 53.1% (2,189 of 4,120) did not have a history of depression prior to pregnancy. Table 1 shows demographics, delivery characteristics and reproductive factors for women with and without major depression during pregnancy according to their history of depression prior to pregnancy. Women who suffered from major depression during pregnancy were more frequently nulliparous, younger, and gave birth by caesarean section, to a male infant, and had a lower mean birth weight compared with women with no depression during pregnancy. Further, they more frequently were smokers, of unspecified SES and had reproductive risk factors, such as prior pregnancy terminations, anaemia, major congenital anomalies, gestational diabetes and maternal pre-existing diabetes, and suffered more frequently from fear of childbirth compared with women with no major depression during pregnancy.

Table 2 shows risk factors for major depression during pregnancy (categories 3 and 4) using women with no major depression without or with a history of depression prior to pregnancy (categories 1 and 2) as a reference population. The strongest risk/associated factors for major depression during pregnancy were a history of depression prior to pregnancy and fear of childbirth, which were associated with a 22.4- and 2.6-fold increased prevalence of major depression during pregnancy, respectively. An increased prevalence of major depression during pregnancy was also associated with adolescent and advanced maternal age, smoking during pregnancy, single marital status, prior

pregnancy terminations of pregnancy, low or unspecified SES, anaemia and gestational diabetes. We performed all the analyses using multiple imputed data, but the results did not change (data not shown).

Pregnancies of women who suffered from major depression during pregnancy more frequently resulted in adverse perinatal outcomes, such as, stillbirth, preterm birth, LBW, SGA, Apgar scores < 7 at 5 minute, fetal venous pH < 7.15 at birth, admission to a neonatal intensive care unit and major congenital anomalies, compared with women without major depression during pregnancy (Table 3). Major depression was not associated with early neonatal death. Smoking appeared to contribute the most to the increased prevalence of SGA, LBW, preterm birth, stillbirth and admission to a neonatal intensive care associated with major depression, but made only a minor contribution to the increased prevalence of other perinatal outcomes, except early neonatal death and low fetal venous pH, associated with major depression during pregnancy. SES made a minor contribution to the increased prevalence of all perinatal outcomes, except admission to a neonatal unit, early neonatal death and low fetal venous pH, associated with major depression during pregnancy.

Discussion

Main findings

The prevalence of major depression during pregnancy among women with singleton births was 0.8%, which is consistent with a previous population- and diagnosis-based study,(2) but substantially lower than 3.1-12.8% reported by smaller studies utilizing mostly self-reported screening or interviews.(14-16) More than half of the episodes occurred in women without a history of depression prior to pregnancy. The second strongest associated factor for major depression

during pregnancy after history of depression was fear of childbirth, which was associated with three-fold increased odds of major depression during pregnancy. Major depression during pregnancy occurred most frequently in women with low or unspecified SES, single marital status and unhealthy behavior, such as smoking. Outcomes of pregnancies were substantially worse than in women with no major depression during pregnancy. Smoking during pregnancy contributed substantially to an increased prevalence of SGA, LBW, preterm birth and admission to a neonatal unit associated with major depression during pregnancy.

Strengths and limitations

The present study has several strengths: the data included the entire childbearing population gathered from three national health registers with high-quality data (17,18) depression during pregnancy was diagnosed by a physician, and some novel risk factors, such as fear of childbirth, were studied. However, we acknowledge several limitations with the present study. Information on depression covered only cases diagnosed and treated in specialized medical care units. We did not have information on women experienced major depression during pregnancy diagnosed treated in primary health care. However, it is likely that most high-risk pregnancies such as women with diagnosed depression were treated in by specialized maternity care, thus providing us information on most women with major depression. Further, information on depression was available only since 1996 for inpatient visits and since 1998 for outpatient visits, and therefore we may not have had complete information on all pre-pregnancy depression episodes. In addition, we had no information on antidepressant medication at an individual level and history of adverse pregnancy outcomes, and thus could not assess their roles as confounders in the multivariable analyses. Further, information on SES could not be defined or was missing for approximately 40% of the births. SES is self-reported and optional, and due to confidentiality concerns, some women chose not provide it. However, the socio-demographics of this group were close to those of the general population, and

multiple data imputations of missing information did not change the results (data not shown). Further, SES was solely defined based on maternal occupation at birth that is related to education and income in Finland, and is an appropriate available indicator for studies on socioeconomic health disparity.(19,20) Further, due to data protection issues we did not have information on spouses' SES. No adjustment was made for multiple comparisons, and model results should be interpreted accordingly.

Interpretation

History of depression prior to pregnancy was the strongest predisposing factor for major depression during pregnancy. However, more than half of the women with major depression during pregnancy had no history of depression indicating that the first episode of depression is not uncommon during pregnancy. A previous systematic review(3) did not report a positive association between a history of depression prior to pregnancy and antenatal depression, but there were only three studies with multivariable analyses. The three previous studies were with small sample size and had heterogeneity in assessment for a prior history of depression.(3) A novel finding of the present study was that physician-diagnosed fear of childbirth was associated with on the order of three-fold increased prevalence of major depression during pregnancy. Several previous studies reported an association between anxiety disorders and major depression during pregnancy as previously reviewed.(3) We showed also that low SES, lack of social support, and unhealthy reproductive behavior, such as smoking, were risk factors for major depression during pregnancy. These results are partly in line with a previous systematic review suggesting that smoking, anxiety symptoms, lower SES, life stress, and lack of social support were associated with an increased prevalence of antepartum depression.(3) Further, the association between gestational diabetes and maternal pre-existing diabetes was in accordance with the results of previous studies.(2,4) However, our results did not confirm the association between preeclampsia and perinatal depression found in previous

studies.(2,5) In general, it has been suggested that depression and other pregnancy morbidities, such as diabetes and preeclampsia, would have a partially common physiological pathway.(21) Risk factors for major depression during pregnancy did not vary substantially between women with and without a history of depression (data not shown).

Our results showed that outcomes of pregnancies affected by major depression during pregnancy were worse than pregnancies not affected by major depression during pregnancy. Several previous studies reviewed found a positive association between preterm birth and depression during pregnancy, but not with other outcomes such as LBW, Apgar scores and admission to NICU.(7) However, the authors suggest that the results might be affected by differences in definition of perinatal outcomes (many studies did not use standard definitions), and that many studies were underpowered or did not have all important covariates such as maternal smoking.(7)

Adverse perinatal outcomes are strongly associated with SES and health behavior such as smoking.(8) In the present study it seemed that smoking mediated the association between adverse perinatal outcomes and depression during pregnancy. Based on previous systematic reviews and meta-analysis, antidepressant medication during pregnancy has been shown to be associated with preterm birth,(22) lower Apgar scores,(22) and poor neonatal adaptation,(23) but not with major congenital anomalies.(24) Further, exposure specifically to SSRIs has been shown to be associated with preterm birth,(25) and low Apgar scores,(26) but not with stillbirth, neonatal mortality or postnatal mortality.(27) A limitation in the present study was that we could not assess the contribution of antidepressant medication to adverse perinatal outcomes associated with depression during pregnancy, since we did not have access to this information on an individual level. Among the total delivering population, the use of selective serotonin reuptake inhibitors (SSRIs) ranged from 0.5% in 1997 to 3.7% in 2010 in Finland.

Conclusions

Using a large nine-year national population-based data on all singleton births, we concluded that physician-diagnosed episodes of major depression in specialized healthcare units during pregnancy were rare. The strongest risk factor for major depression was history of depression prior to pregnancy. This result may help clinicians to recognize the risk of depression. Other risk factors for major depression during pregnancy were low SES, lack of social support and unhealthy behavior during pregnancy, such as smoking. Major depression was also associated with fear of childbirth. Outcomes of pregnancies among women affected by major depression during pregnancy were worse than in unaffected women, but smoking during pregnancy made a substantial or modest contribution to the increased prevalence of SGA, LBW, preterm and admission to a neonatal unit associated with depression during pregnancy. Furthermore, its of note that women with history of depression prior to pregnancy or major depression during pregnancy are more likely to experience postpartum depression,(28,29) and consequences of postpartum depression might be more severe for women, since it has shown to be associated with an increased risk of self-harm such as suicide.(30,31) Therefore, because of possible severe maternal and fetal consequences and high risk of relapse, treatment of antepartum depression should be managed actively by a multi-professional team.

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Data sharing: No additional data available.

Contributor statement

All authors participated in designing the study. SR managed the dataset and performed statistical analyses. SML, HSN, MG, MRK and SH were statistical advisors. All authors contributed to the interpretation of the results, as well as to writing and editing the manuscrip

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Table 1. Delivery characteristics and reproductive risk factors among women with singleton pregnancies with and without major depression during pregnancy and with and without a history of depression prior to pregnancy from 2002 to 2010 in Finland.

Characteristic	No major depression during pregnancy, *n*=493,037 (96.3%)	No major depression during pregnancy, *n*= 14,781 (2.9%)	Major depression during pregnancy, *n*=2,189 (0.4%)	Major depression during pregnancy, *n*=1,931 (0.4%)	*p value**
A history of depression prior to pregnancy	No	Yes	No	Yes	
Nulliparous % Multiparous	42.0 58.0	45.1 54.9	45.5 54.5	50.0 50.0	*≤0.001*
Mean maternal age, years (SD)	29.6 (5.4)	27.6 (6.0)	28.4 (6.2)	28.7 (6.6)	≤0.001
Mean gestational age, wk (SD)	39.8 (1.8)	39.7 (1.9)	39.4 (2.0)	39.5 (2.0)	≤0.001
Mode of delivery % Vaginal spontaneous Breech Forceps Vacuum assistance Caesarean section	 75.8 0.6 0.1 7.2 15.9	 74.8 0.6 0.1 7.5 17.1	 72.6 0.2 0.1 7.5 19.6	 70.4 0.4 0.0 7.7 21.5	≤0.001
Mean birth weight, g (SD)	3531.4 (550)	3479.0 (568)	3453.1 (580)	3456.3 (608)	≤0.001
Male fetal sex %	51.2	50.0	51.1	51.8	0.04
Major congenital anomalies %	4.0	5.2	5.6	5.9	≤0.001
Smoking status % Non-smoking Quit smoking during 1st trimester Smoking after 1st trimester Missing information	 83.2 3.7 10.5 2.6	 63.4 6.9 26.7 2.9	 66.1 6.5 25.1 2.3	 59.5 8.3 29.3 3.0	≤0.001
Married or living with a partner %	93.5	86.3	83.1	83.0	≤0.001
Socioeconomic status % Upper white-collar worker Lower white-collar worker Blue-collar worker Others [a] Missing information	 8.6 34.5 14.2 25.7 17.2	 3.7 25.8 16.0 31.0 23.6	 4.0 27.9 14.9 31.9 21.3	 3.8 25.5 15.3 30.0 25.3	≤0.001
Prior miscarriages %	20.7	23.6	23.3	23.2	≤0.001
Prior terminations %	12.2	22.4	19.8	21.7	≤0.001
In vitro fertilization (IVF) %	1.6	1.2	0.9	1.3	≤0.001
Anaemia, ≤100 g/L %	1.6	2.6	3.5	2.8	≤0.001
Placenta praevia %	0.3	0.2	0.2	0.4	0.54

Placental abruption %	0.3	0.4	0.5	0.7	0.07
Preeclampsia %	1.2	1.3	0.9	1.2	0.52
Gestational diabetes %	11.2	13.4	14.5	17.6	≤0.001
Pre-existing diabetes %	8.4	10.9	11.6	13.6	≤0.001
Prior caesarean section %	10.6	10.5	10.3	10.2	0.90
Fear of childbirth %	4.6	11.4	15.0	17.5	≤0.001

SD=standard deviation, *chi-square or Kruskal-Wallis test, [a] 'Others' comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases,

Table 2. Unadjusted and adjusted odds ratios (aOR) of major depression during pregnancy among women with singleton pregnancies from 2002-2010 in Finland using women with no major depression during pregnancy without and with a history of depression prior to pregnancy as a reference population (categories 1 and 2).

Characteristic	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)
A history of depression prior to pregnancy	29.43 (27.62-31.35)	22.36 (20.86-23.98)
Maternal age (years)		
≤19	3.14 (2.79-3.52)	1.58 (1.38-1.81)
20–29	1	1
30–39	0.86 (0.81-0.92)	1.19 (1.11-1.28)
≥40	1.41 (1.22-1.63)	1.65 (1.41-1.94)
Nulliparous women	1.25 (1.18-1.33)	1.21 (1.12-1.30)
Multiparous women	1	1
Smoking status		
Non-smoking	1	1
Quit smoking during 1st trimester	2.52 (2.23-2.84)	1.57 (1.38-1.80)
Smoking after 1st trimester	3.25 (3.03-3.49)	1.67 (1.53-1.81)
Missing information	1.32 (1.09-1.60)	1.09 (0.88-1.35)
Married/living with a partner	1	1
Single	2.86 (2.62-3.11)	1.63 (1.48-1.79)
Socioeconomic status		
Upper white-collar worker	1	1
Lower white-collar worker	1.69 (1.43-1.99)	1.42 (1.20-1.69)
Blue-collar worker	2.29 (1.93-2.73)	1.53 (1.27-1.84)
Others [a]	2.59 (2.20-3.05)	1.67 (1.40-1.98)
Missing information	2.88 (2.43-3.40)	1.66 (1.39-1.98)
Prior miscarriages	1.15 (1.07-1.24)	1.09 (1.00-1.18)
Prior terminations	1.82 (1.69-1.97)	1.14 (1.04-1.24)
In vitro fertilization (IVF)	0.70 (0.53-0.94)	0.78 (0.58-1.07)
Anaemia ≤100 g/L	2.02 (1.70-2.41)	1.49 (1.22-1.81)
Gestational diabetes	1.49 (1.37-1.62)	1.29 (1.11-1.50)
Pre-existing diabetes	1.56 (1.42-1.71)	1.10 (0.93-1.31)
Fear of childbirth	3.80 (3.49-4.13)	2.63 (2.39-2.89)
Male fetal sex	1.01 (0.95-1.07)	0.97 (0.91-1.04)

*ORs of major depression adjusted by history of depression prior to pregnancy, maternal age, parity, smoking status, marital status, SES, prior miscarriages, prior terminations, IVF, anaemia, gestational diabetes, pre-existing diabetes, fear of childbirth, and fetal sex.

[a] Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases, CI=confidence interval

Table 3. Adjusted odds ratios (ORs) of major depression during pregnancy associated with adverse perinatal outcomes among singleton births in Finland from 2002-2010.

Perinatal outcome	**Model 1** adjusted by major depression during pregnancy	**Model 2** adjusted by Model 1 + age and parity	**Model 3** adjusted by Model 2 + socioeconomic status (SES)	**Model 4** adjusted by Model 2 + smoking	**Model 5** adjusted by Model 2 + SES and smoking
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Admission to a NICU	1.79 (1.65-1.95)	1.78 (1.64-1.94)	1.78 (1.64-1.93)	1.68 (1.55-1.83)	1.69 (1.55-1.84)
Stillbirth	1.97 (1.33-2.93)	2.01 (1.35-2.99)	1.86 (1.25-2.76)	1.88 (1.27-2.80)	1.77 (1.19-2.63)
Early neonatal death	1.08 (0.49-2.42)	1.13 (0.50-2.51)			
Preterm birth (<37 weeks)	1.57 (1.39-1.77)	1.57 (1.39-1.77)	1.55 (1.37-1.75)	1.49 (1.32-1.68)	1.48 (1.31-167)
LBW (<2500 grams)	1.56 (1.36-1.79)	1.55 (1.35-1.79)	1.53 (1.33-1.76)	1.37 (1.19-1.58)	1.36 (1.18-1.56)
SGA (<-2 SD below mean birth weight)	1.46 (1.27-1.67)	1.41 (1.23-1.62)	1.39 (1.21-1.59)	1.18 (1.03-1.36)	1.17 (1.02-1.35)
Apgar scores (<7 at 5 minute) [a]	2.13 (1.79-2.54)	2.11 (1.77-2.51)	2.07 (1.74-2.47)	2.05 (1.72-2.45)	2.02 (1.70-2.41)
Fetal venous pH <7.15 at birth [a, b]	1.37 (1.06-1.76)	1.32 (1.03-1.71)	1.33 (1.03-1.72)	1.35 (1.05-1.74)	1.36 (1.06-1.76)
Major congenital anomaly	1.47 (1.29-1.67)	1.48 (1.29-1.69)	1.47 (1.29-1.68)	1.44 (1.26-1.65)	1.44 (1.26-1.64)

[a] available since 2004, [b] gathered selectively by indication, NICU= neonatal intensive care unit, LBW= low birth weight, SGA= small for gestational age, CI=confidence interval

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
D **Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **OK**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **OK**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **OK**
Objectives	3	State specific objectives, including any prespecified hypotheses **OK**
Methods		
Study design	4	Present key elements of study design early in the paper **OK**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **OK**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **OK**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **NA**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **OK**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **OK**
Bias	9	Describe any efforts to address potential sources of bias **OK**
Study size	10	Explain how the study size was arrived at **TOTAL POPULATION**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **OK**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **OK**
		(*b*) Describe any methods used to examine subgroups and interactions **OK**
		(*c*) Explain how missing data were addressed **OK**
		(*d*) If applicable, explain how loss to follow-up was addressed **NO**
		(*e*) Describe any sensitivity analyses **OK**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **OK**
		(b) Give reasons for non-participation at each stage **NO**
		(c) Consider use of a flow diagram **NA**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **OK**
		(b) Indicate number of participants with missing data for each variable of interest **OK**
		(c) Summarise follow-up time (eg, average and total amount) **OK**
Outcome data	15*	Report numbers of outcome events or summary measures over time **OK**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included **OK**
		(*b*) Report category boundaries when continuous variables were categorized OK
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **OK**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **OK**
Discussion		
Key results	18	Summarise key results with reference to study objectives **OK**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **OK**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **OK**
Generalisability	21	Discuss the generalisability (external validity) of the study results **OK**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **OK**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Risk factors for and perinatal outcomes of major depression during pregnancy – a population-based analysis during 2002-2010 in Finland

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Risk factors for and perinatal outcomes of major depression during pregnancy – a population-based analysis during 2002-2010 in Finland

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Keywords: Childbirth, Depression, Population Register, Register, Socioeconomic Status

Word count: 3465

Abstract

Objectives: To identify risk factors for and the consequences (several adverse perinatal outcomes) of physician-diagnosed major depression during pregnancy treated in specialized healthcare.

Design: A population-based cross sectional study

Setting: Data were gathered from Finnish health registers for 1996-2010.

Participants: All singleton births (*n*=511,938) for 2002-2010 in Finland

Primary outcome measures: Prevalence, risk factors and consequences of major depression during pregnancy

Results: Among 511,938 women, 0.8% experienced major depression during pregnancy, of which 46.9% had a history of depression prior to pregnancy. After history of depression the second strongest associated factor for major depression was fear of childbirth, with a 2.6-fold (adjusted odds ratio (aOR=2.63, 95% confidence interval (CI)=2.39-2.89) increased prevalence. The risk profile of major depression also included adolescent or advanced maternal age, low or unspecified socioeconomic status (SES), single marital status, smoking, prior pregnancy terminations, anaemia and gestational diabetes regardless of a history of depression. Outcomes of pregnancies were worse among women with than without major depression. The contribution of smoking was substantial to modest for small for gestational age newborn (< -2 standard deviation below mean birth), low birth weight (< 2,500 g), preterm birth (<37 weeks) and admission to neonatal intensive care associated with major depression was, whereas SES made only a minor contribution.

Conclusions: Physician-diagnosed major depression during pregnancy was found to be rare. The strongest risk factor was history of depression prior to pregnancy. Other associated factors were fear of childbirth, low SES, lack of social support and unhealthy reproductive behavior such as

smoking. Outcomes of pregnancies were worse among women with than without major depression. Smoking during pregnancy made a substantial to modest contribution to adverse outcomes associated with depression during pregnancy.

Article summary

Article focus

- To identify risk factors for and the consequences of physician-diagnosed major depression during pregnancy defined according to the International Classification of Diseases (ICD) - 10 codes during pregnancy.

Key messages

- After history of depression prior to pregnancy the strongest associated factor for major depression during pregnancy was physician-diagnosed fear of childbirth.

- Outcomes of pregnancies were worse among women with than without major depression.

Strengths and limitations

- Strengths of this study were the population-based data gathered from three mandatory national health registers, and physician-diagnosed depression defined by ICD-10 codes.

- Possible limitations were that we did not have information on women diagnosed and treated for major depression during pregnancy in primary health care, information on history of depression was based on outpatient and inpatient visits only since 1998 and 1996, respectively, and we did not have information on antidepressant medication at an individual level.

Introduction

Depression is globally one of the leading causes of disease burden for women.(1) A previous large population-based study reported that 0.8% of 32.2 million women had physician-diagnosed depression at the time of delivery in United States (US) during 1998-2005.(2) A recent systematic review concluded that according to multivariable analyses, life stress, lack of social support and domestic violence were associated with an increased risk of depression during pregnancy, whereas maternal anxiety, history of depression, unintended pregnancy, lack of private medical insurance, low income, low education, smoking, single marital status and poor relationship were only significant predictors in bivariable analysis.(3) The authors of this review highlighted several limitations of previous studies, such as differences in the methods used to screen depression, study population, risk factors and confounders included in statistical analyses. It has been suggested that use of self-reported screening methods may overestimate the prevalence of depression, which in turn suggests that their sensitivity and specificity are not adequate.(4) Further, several previous studies have shown that diabetes mellitus, gestational diabetes,(2,5) preeclampsia,(2,6) anaemia, caesarean section and placental abnormalities(2) are more prevalent among women suffering from perinatal depression.

Antepartum and postpartum depression represent a risk for children's short- and long-term wellbeing.(7) Several studies have reported an association between antepartum depression and risk of preterm birth, but no association with other adverse outcomes, such as low birth weight, admission to a neonatal intensive care unit and low Apgar scores, as shown in a systematic review and meta-analysis.(8) However, many of these studies were potentially underpowered because of small sample sizes and were also heterogeneous with respect to the study population and analyses. Further, the use of different methods to measure and define depression raises questions about whether all studies really measured clinically diagnosed major depression.(8) Further, the previous

mentioned large population-based study from US found that physician-diagnosed depression at the time of birth was associated with an increased prevalence of preterm birth, fetal growth restriction, fetal abnormalities, fetal distress and fetal death.(2)

The aim of the present large population based cross sectional study was to identify risk factors for major depression during pregnancy based on ICD-10 codes (International Classification of Diseases) treated in specialized healthcare units, especially an association between a prior history of depression and antepartum depression that was only studied by few smaller studies.(3) Furthermore, we studied whether major depression during pregnancy was associated with adverse perinatal outcomes and the degree to which this association was attenuated by women's SES and smoking (strongly associated with adverse perinatal outcomes)(9) during pregnancy in Finland. Most previous studies considering an association between adverse perinatal outcomes and depression were small and population based studies were scarce.(8) Further, differences in health care services such as access to antenatal care might limit generalizability of the large previous study from US.(2) In Finland, with around 5.5 million residents, health care services are mainly publicly funded and all women have free access to antenatal care.

Materials and Methods

Data and population

Data were gathered from three national health registers currently maintained by the National Institute for Health and Welfare and were linked using women's encrypted unique personal identification numbers. The Finnish MBR contains demographics, pregnancy and delivery characteristics and diagnoses on all live births or stillbirths delivered after the 22nd gestational week or weighing 500 g or more during the first postnatal week recorded since 1987. The MBR data was supplemented by information on maternal health (major depression, preeclampsia,

gestational diabetes, pre-existing diabetes, and fear of childbirth) gathered and defined based on ICD-10 codes from the Hospital Discharge Register (HDR). The HDR was established in 1969 and contains information on all aspects of inpatient care and outpatient visits in Finnish hospitals. Information on major congenital anomalies (yes or no) was gathered and the Register of Congenital Malformations established 1963. Data included all women with singleton births (*n*=511,938) from 2002-2010; multiple births (*n*=15,767) were excluded because they carry a higher risk of complications. The present time period was chosen since information on depression (i.e., a history of depression prior to pregnancy) was available since 1996 for inpatient visits and since 1998 for outpatient visits.

The National Institute for Health and Welfare approved study plan and use of the data for the study as required by the national data protection legislation in Finland (Reference number 1749/5.05.00/2011).

Variables and definitions

Depression, physician-diagnosed, was defined by ICD-10 codes F31.3, F31.5 and F32-34 and women were grouped into four categories; 1) no major depression during pregnancy, and no history of depression prior to pregnancy, 2) no major depression during pregnancy with a history of depression prior to pregnancy, 3) major depression during pregnancy with no history of depression prior to pregnancy, and 4) major depression during pregnancy with a history of depression prior to pregnancy. Information on major depression was based on outpatient visits (patients without overnight hospitalization) in specialized health care since 1998 and inpatient visits (at least an overnight stay at a hospital) specialized health care since 1996 gathered from the HDR. In Finland, general practitioners and midwives in health care centers provide primary health care such as antenatal care, and specialists in regional and university teaching hospitals provide specialized health care. Health care professionals at both levels are instructed to evaluate the mother's mental

wellbeing as part of all appointments. Parity was categorized as either nulliparous, if women had no prior births, or multiparous, if women had at least one prior birth. The gestational age was estimated based on first- or second-trimester ultrasonography measurements. Mode of delivery was classified as vaginal spontaneous, breech, forceps, vacuum assisted or caesarean section (CS). Smoking habits during pregnancy based on self-reported information was grouped into three categories: non-smoking, quitted smoking during the first trimester, and continued smoking after the first trimester, i.e., smoking. Marital status was classified as either married (including women living with a partner) or single. SES was grouped into five categories based on the Finnish Classification of Occupations(10) which was developed according to international recommendations: upper white-collar workers, such as physicians and lawyers; lower white-collar workers, such as nurses and secretaries; blue-collar workers, such as cooks and cashiers; others; and missing information, as categorized and published elsewhere.(11) 'Others' comprised 25.9% (*n*=132,391) of all cases and included all births with unspecified occupations, such as entrepreneurs, students, retired, unemployed and housewives. The category with missing SES information comprised 17.4% (*n*=89,041) of all births. Information on prior CS, induction, miscarriages and pregnancy terminations was dichotomous (yes or no). Information on in vitro fertilization (IVF) included intracytoplasmic sperm injection and frozen embryo transfers. Anaemia was defined as hemoglobin levels ≤100 g/L. Placenta praevia (O44), placental abruption (O45), preeclampsia (O14 and O15), gestational diabetes (O24.4), and maternal preexisting diabetes (O24.0 and O24.1) were gathered from the HDR based on ICD-10 codes. Fear of childbirth was defined by national ICD-10 code O99.80. Feelings towards childbirth are asked all women in antenatal care and women experiencing significant fear of childbirth that cannot be counseled during antenatal visits in primary health care or making CS request due to fear of childbirth are referred to specialist maternity care as described previously.(12,13)

Adverse perinatal outcomes: Admission to a neonatal intensive care unit (NICU) was defined as at least 24 hour surveillance at neonatal intensive care. Stillbirth was defined as fetal death from 22 gestational weeks onwards or birth weight 500 grams or more and early neonatal death as death during the first seven postnatal days. Preterm birth was defined as gestational age < 37+0 weeks. Low birth weight (LBW) was defined as a birth weight of less than 2,500 grams. Small for gestational age (SGA) was defined as a sex- and parity-specific birth weight more than two standard deviation (SD) below the mean weight for gestational based on the national 2013 population-based reference.(14) Five minute Apgar scores < 7 and infant's vein pH < 7.15 were considered low (taken by indication and both available since 2004).

Statistical analyses

Differences between the four categories of women defined by their depression history as described previously were evaluated by chi-square test for dichotomous or categorical variables and Kruskal-Wallis test for continuous variables. Unadjusted and adjusted odds ratios (ORs) of major depression were determined by using logistic regression analyses. The outcome event of interest was major depression during pregnancy (categories 3 and 4), and the reference group was all women without major depression without or with a history of depression prior to pregnancy (categories 1 and 2). All covariates were determined based on literature and results of bivariable analyses.

To address the second research aim regarding the contribution of major depression to adverse perinatal outcomes with or without further control for smoking, SES and other covariates, a second set of logistic models was fitted. For each perinatal outcome, a preliminary model (Model 1) was used to estimate the association between major depression and perinatal outcome. Then, additional covariates were added in subsequent models: adjustment for age and parity (Model 2), adjustment for Model 2 variables plus SES (Model 3), adjustment for Model 2 variables plus smoking (Model 4), and adjustment for all variables simultaneously (Model 5). Furthermore, multiple imputations

were performed to study whether missing information on SES affected our results of logistic regression analysis. The data were analyzed using SPSS for Windows 19.0, Chicago, IL. Differences were deemed to be significant if $p < 0.05$. In addition, 95% confidence intervals (CIs) were calculated.

Results

In total, 0.8% (*n*=4,120) of 511,938 women with singleton pregnancy suffered from major depression during pregnancy as diagnosed by ICD-10 codes in specialized healthcare units. Of all the women with major depression during pregnancy, 53.1% (2,189 of 4,120) did not have a history of depression prior to pregnancy. Table 1 shows demographics, delivery characteristics and reproductive factors for women with and without major depression during pregnancy according to their history of depression prior to pregnancy. Women who suffered from major depression during pregnancy were more frequently nulliparous, younger, and gave birth by caesarean section, to a male infant, and had a lower mean birth weight compared with women with no depression during pregnancy. Further, they more frequently were smokers, of unspecified SES and had reproductive risk factors, such as prior pregnancy terminations, anaemia, major congenital anomalies, gestational diabetes and maternal pre-existing diabetes, and suffered more frequently from fear of childbirth compared with women with no major depression during pregnancy.

Table 2 shows risk factors for major depression during pregnancy (categories 3 and 4) using women with no major depression without or with a history of depression prior to pregnancy (categories 1 and 2) as a reference population. The strongest risk/associated factors for major depression during pregnancy were a history of depression prior to pregnancy and fear of childbirth, which were associated with a 22.4- and 2.6-fold increased prevalence of major depression during pregnancy, respectively. An increased prevalence of major depression during pregnancy was also associated with adolescent and advanced maternal age, smoking during pregnancy, single marital status, prior

pregnancy terminations of pregnancy, low or unspecified SES, anaemia and gestational diabetes. We performed all the analyses using multiple imputed data, but the results did not change (data not shown).

Pregnancies of women who suffered from major depression during pregnancy more frequently resulted in adverse perinatal outcomes, such as, stillbirth, preterm birth, LBW, SGA, Apgar scores < 7 at 5 minute, fetal venous pH < 7.15 at birth, admission to a neonatal intensive care unit and major congenital anomalies, compared with women without major depression during pregnancy (Table 3). Major depression was not associated with early neonatal death. Smoking appeared to contribute the most to the increased prevalence of SGA, LBW, preterm birth, stillbirth and admission to a neonatal intensive care associated with major depression, but made only a minor contribution to the increased prevalence of other perinatal outcomes, except early neonatal death and low fetal venous pH, associated with major depression during pregnancy. SES made a minor contribution to the increased prevalence of all perinatal outcomes, except admission to a neonatal unit, early neonatal death and low fetal venous pH, associated with major depression during pregnancy.

Discussion

Main findings

The prevalence of major depression during pregnancy among women with singleton births was 0.8%, which is consistent with a previous population- and diagnosis-based study,(2) but substantially lower than 3.1-12.8% reported by smaller studies utilizing mostly self-reported screening or interviews.(15-17) This finding is likely to indicate that self-reported screening methods such as the Edinburg Depression Scale (EDPS) are likely to be sensitive to early mental

health concerns and may overestimate prevalence of depression.(18) Furthermore, self-reported screening methods are not adequate to predict only depressive symptoms; they are suggested to be sensitive also for anxiety and stress-related symptoms.(4,18) More than half of the depression episodes occurred in women without a history of depression prior to pregnancy. The second strongest associated factor for major depression during pregnancy after history of depression was fear of childbirth, which was associated with three-fold increased odds of major depression during pregnancy. Major depression during pregnancy occurred most frequently in women with low or unspecified SES, single marital status and unhealthy behavior, such as smoking. Outcomes of pregnancies in women with major depression were substantially worse than in women with no major depression during pregnancy. Smoking during pregnancy contributed substantially to an increased prevalence of SGA, LBW, preterm birth and admission to a neonatal unit associated with major depression during pregnancy.

Strengths and limitations

The present study has several strengths: the data included the entire childbearing population gathered from three national health registers with high-quality data(19,20) depression during pregnancy was diagnosed by a physician, and some novel risk factors, such as fear of childbirth, were studied. However, we acknowledge several limitations with the present study. Information on depression covered only cases diagnosed and treated in specialized medical care units. We did not have information on women experienced major depression during pregnancy diagnosed treated in primary health care. However, it is likely that most high-risk pregnancies such as women with diagnosed depression were treated in by specialized maternity care, thus providing us information on most women with major depression. Further, information on depression was available only since 1996 for inpatient visits and since 1998 for outpatient visits, and therefore we may not have had complete information on all pre-pregnancy depression episodes. It is also of note that maternal

perinatal mental health is influenced by several factors such as parental relationship (such as domestic violence), substance abuse, and personal characteristics not studied in the present study. It has been suggested that depressive, anxiety and stress-related symptoms are much more common than doctor diagnosed disorders such as depression and anxiety.(4,18) However, we did not have information on all possible confounders and other maternal mental health concerns such as anxiety and stress-related diagnosed disorders. In addition, we had no information on antidepressant medication at an individual level and history of adverse pregnancy outcomes, and thus could not assess their roles as confounders in the multivariable analyses. Further, information on SES could not be defined or was missing for approximately 40% of the births. SES is self-reported and optional, and due to confidentiality concerns, some women chose not provide it. However, the socio-demographics (such as smoking, maternal age, and parity) of this group were close to those of the general population, and multiple data imputations of missing information did not change the results (data not shown). Further, SES was solely defined based on maternal occupation at birth that is related to education and income in Finland, and is an appropriate available indicator for studies on socioeconomic health disparity.(21,22) Further, due to data protection issues we did not have information on spouses' SES. No adjustment was made for multiple comparisons, and model results should be interpreted accordingly.

Interpretation

History of depression prior to pregnancy was the strongest predisposing factor for major depression during pregnancy. However, more than half of the women with major depression during pregnancy had no history of depression indicating that the first episode of depression is not uncommon during pregnancy. A previous systematic review(3) did not report a positive association between a history of depression prior to pregnancy and antenatal depression, but there were only three studies with multivariable analyses. The three previous studies were with small sample size and had

heterogeneity in assessment for a prior history of depression.(3) A novel finding of the present study was that physician-diagnosed fear of childbirth was associated with on the order of three-fold increased prevalence of major depression during pregnancy. Several previous studies reported an association between anxiety disorders and major depression during pregnancy as previously reviewed.(3) We showed also that low SES, lack of social support, and unhealthy reproductive behavior, such as smoking, were risk factors for major depression during pregnancy. These results are partly in line with a previous systematic review suggesting that smoking, anxiety symptoms, lower SES, life stress, and lack of social support were associated with an increased prevalence of antepartum depression.(3) Further, the association between gestational diabetes and maternal pre-existing diabetes was in accordance with the results of previous studies.(2,5) However, our results did not confirm the association between preeclampsia and perinatal depression found in previous studies.(2,6) In general, it has been suggested that depression and other pregnancy morbidities, such as diabetes and preeclampsia, would have a partially common physiological pathway.(23) Risk factors for major depression during pregnancy did not vary substantially between women with and without a history of depression (data not shown).

Our results showed that outcomes of pregnancies affected by major depression during pregnancy were worse than pregnancies not affected by major depression during pregnancy. Several previous studies reviewed found a positive association between preterm birth and depression during pregnancy, but not with other outcomes such as LBW, Apgar scores and admission to NICU.(8) However, the authors suggest that the results might be affected by differences in definition of perinatal outcomes (many studies did not use standard definitions), and that many studies were underpowered or did not have all important covariates such as maternal smoking.(8)

Adverse perinatal outcomes are strongly associated with SES and health behavior such as smoking. (9) In the present study it seemed that smoking mediated the association between adverse perinatal

outcomes and depression during pregnancy. However, whether there is causation between smoking and depression and how these are linked, i.e., whether depression leads to smoking or smoking alters the risk of depression, could not be fully evaluated in the present setting; thus exact meditational analyses were not conducted. Based on previous systematic reviews and meta-analysis, antidepressant medication during pregnancy has been shown to be associated with preterm birth,(24) lower Apgar scores,(24) and poor neonatal adaptation,(25) but not with major congenital anomalies.(26) Further, exposure specifically to SSRIs has been shown to be associated with preterm birth,(27) and low Apgar scores,(28) but not with stillbirth, neonatal mortality or postnatal mortality.(29) A limitation in the present study was that we could not assess the contribution of antidepressant medication to adverse perinatal outcomes associated with depression during pregnancy, since we did not have access to this information on an individual level. Among the total delivering population, the use of selective serotonin reuptake inhibitors (SSRIs) ranged from 0.5% in 1997 to 3.7% in 2010 in Finland.

Conclusions

Using a large nine-year national population-based data on all singleton births, we concluded that physician-diagnosed episodes of major depression in specialized healthcare units during pregnancy were rare. Maternal perinatal mental health is a complex issue and influenced by several psychosocial factors, and it has been shown that depressive, anxiety and other stress-related symptoms measured by self-reported screening, not studied in the present study, have been suggested to be much more common than diagnosed disorders such as perinatal depression. The strongest risk factor for major depression was history of depression prior to pregnancy. This result may help clinicians to recognize the risk of depression. Other risk factors for major depression during pregnancy were low SES, lack of social support and unhealthy behavior during pregnancy, such as smoking. Major depression was also associated with fear of childbirth. Outcomes of

pregnancies among women affected by major depression during pregnancy were worse than in unaffected women, but smoking during pregnancy made a substantial or modest contribution to the increased prevalence of SGA, LBW, preterm and admission to a neonatal unit associated with depression during pregnancy. Furthermore, its of note that women with history of depression prior to pregnancy or major depression during pregnancy are more likely to experience postpartum depression,(30,31) and consequences of postpartum depression might be more severe for women, since it has shown to be associated with an increased risk of self-harm such as suicide.(32,33) Therefore, because of possible severe maternal and fetal consequences and high risk of relapse, treatment of antepartum depression should be managed actively by a multi-professional team.

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Contributor statement

All authors participated in designing the study. SR managed the dataset and performed statistical analyses. SML, HSN, MG, MRK and SH were statistical advisors. All authors contributed to the interpretation of the results, as well as to writing and editing the manuscrip

Competing interests: None.

Data sharing: No additional data available.

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Table 1. Delivery characteristics and reproductive risk factors among women with singleton pregnancies with and without major depression during pregnancy and with and without a history of depression prior to pregnancy from 2002 to 2010 in Finland.

Characteristic	No major depression during pregnancy, *n*=493,037 (96.3%)	No major depression during pregnancy, *n*= 14,781 (2.9%)	Major depression during pregnancy, *n*=2,189 (0.4%)	Major depression during pregnancy, *n*=1,931 (0.4%)	*p value**
A history of depression prior to pregnancy	No	Yes	No	Yes	
Nulliparous % Multiparous	42.0 58.0	45.1 54.9	45.5 54.5	50.0 50.0	*≤0.001*
Mean maternal age, years (SD)	29.6 (5.4)	27.6 (6.0)	28.4 (6.2)	28.7 (6.6)	≤0.001
Mean gestational age, wk (SD)	39.8 (1.8)	39.7 (1.9)	39.4 (2.0)	39.5 (2.0)	≤0.001
Mode of delivery % Vaginal spontaneous Breech Forceps Vacuum assistance Caesarean section	 75.8 0.6 0.1 7.2 15.9	 74.8 0.6 0.1 7.5 17.1	 72.6 0.2 0.1 7.5 19.6	 70.4 0.4 0.0 7.7 21.5	≤0.001
Mean birth weight, g (SD)	3531.4 (550)	3479.0 (568)	3453.1 (580)	3456.3 (608)	≤0.001
Male fetal sex %	51.2	50.0	51.1	51.8	0.04
Major congenital anomalies %	4.0	5.2	5.6	5.9	≤0.001
Smoking status % Non-smoking Quit smoking during 1st trimester Smoking after 1st trimester Missing information	 83.2 3.7 10.5 2.6	 63.4 6.9 26.7 2.9	 66.1 6.5 25.1 2.3	 59.5 8.3 29.3 3.0	≤0.001
Married or living with a partner %	93.5	86.3	83.1	83.0	≤0.001
Socioeconomic status % Upper white-collar worker Lower white-collar worker Blue-collar worker Others [a] Missing information	 8.6 34.5 14.2 25.7 17.2	 3.7 25.8 16.0 31.0 23.6	 4.0 27.9 14.9 31.9 21.3	 3.8 25.5 15.3 30.0 25.3	≤0.001
Prior miscarriages %	20.7	23.6	23.3	23.2	≤0.001
Prior terminations %	12.2	22.4	19.8	21.7	≤0.001
In vitro fertilization (IVF) %	1.6	1.2	0.9	1.3	≤0.001
Anaemia, ≤100 g/L %	1.6	2.6	3.5	2.8	≤0.001
Placenta praevia %	0.3	0.2	0.2	0.4	0.54

Placental abruption %	0.3	0.4	0.5	0.7	0.07
Preeclampsia %	1.2	1.3	0.9	1.2	0.52
Gestational diabetes %	11.2	13.4	14.5	17.6	≤0.001
Pre-existing diabetes %	8.4	10.9	11.6	13.6	≤0.001
Prior caesarean section %	10.6	10.5	10.3	10.2	0.90
Fear of childbirth %	4.6	11.4	15.0	17.5	≤0.001

SD=standard deviation, *chi-square or Kruskal-Wallis test, [a] 'Others' comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases,

Table 2. Unadjusted and adjusted odds ratios (aOR) of major depression during pregnancy among women with singleton pregnancies from 2002-2010 in Finland using women with no major depression during pregnancy without and with a history of depression prior to pregnancy as a reference population (categories 1 and 2).

Characteristic	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)
A history of depression prior to pregnancy	29.43 (27.62-31.35)	22.36 (20.86-23.98)
Maternal age (years)		
≤19	3.14 (2.79-3.52)	1.58 (1.38-1.81)
20–29	1	1
30–39	0.86 (0.81-0.92)	1.19 (1.11-1.28)
≥40	1.41 (1.22-1.63)	1.65 (1.41-1.94)
Nulliparous women	1.25 (1.18-1.33)	1.21 (1.12-1.30)
Multiparous women	1	1
Smoking status		
Non-smoking	1	1
Quit smoking during 1st trimester	2.52 (2.23-2.84)	1.57 (1.38-1.80)
Smoking after 1st trimester	3.25 (3.03-3.49)	1.67 (1.53-1.81)
Missing information	1.32 (1.09-1.60)	1.09 (0.88-1.35)
Married/living with a partner	1	1
Single	2.86 (2.62-3.11)	1.63 (1.48-1.79)
Socioeconomic status		
Upper white-collar worker	1	1
Lower white-collar worker	1.69 (1.43-1.99)	1.42 (1.20-1.69)
Blue-collar worker	2.29 (1.93-2.73)	1.53 (1.27-1.84)
Others [a]	2.59 (2.20-3.05)	1.67 (1.40-1.98)
Missing information	2.88 (2.43-3.40)	1.66 (1.39-1.98)
Prior miscarriages	1.15 (1.07-1.24)	1.09 (1.00-1.18)
Prior terminations	1.82 (1.69-1.97)	1.14 (1.04-1.24)
In vitro fertilization (IVF)	0.70 (0.53-0.94)	0.78 (0.58-1.07)
Anaemia ≤100 g/L	2.02 (1.70-2.41)	1.49 (1.22-1.81)
Gestational diabetes	1.49 (1.37-1.62)	1.29 (1.11-1.50)
Pre-existing diabetes	1.56 (1.42-1.71)	1.10 (0.93-1.31)
Fear of childbirth	3.80 (3.49-4.13)	2.63 (2.39-2.89)
Male fetal sex	1.01 (0.95-1.07)	0.97 (0.91-1.04)

*ORs of major depression adjusted by history of depression prior to pregnancy, maternal age, parity, smoking status, marital status, SES, prior miscarriages, prior terminations, IVF, anaemia, gestational diabetes, pre-existing diabetes, fear of childbirth, and fetal sex.

[a] Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases, CI=confidence interval

Table 3. Adjusted odds ratios (ORs) of major depression during pregnancy associated with adverse perinatal outcomes among singleton births in Finland from 2002-2010.

Perinatal outcome	**Model 1** adjusted by major depression during pregnancy	**Model 2** adjusted by Model 1 + age and parity	**Model 3** adjusted by Model 2 + socioeconomic status (SES)	**Model 4** adjusted by Model 2 + smoking	**Model 5** adjusted by Model 2 + SES and smoking
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Admission to a NICU	1.79 (1.65-1.95)	1.78 (1.64-1.94)	1.78 (1.64-1.93)	1.68 (1.55-1.83)	1.69 (1.55-1.84)
Stillbirth	1.97 (1.33-2.93)	2.01 (1.35-2.99)	1.86 (1.25-2.76)	1.88 (1.27-2.80)	1.77 (1.19-2.63)
Early neonatal death	1.08 (0.49-2.42)	1.13 (0.50-2.51)			
Preterm birth (<37 weeks)	1.57 (1.39-1.77)	1.57 (1.39-1.77)	1.55 (1.37-1.75)	1.49 (1.32-1.68)	1.48 (1.31-167)
LBW (<2500 grams)	1.56 (1.36-1.79)	1.55 (1.35-1.79)	1.53 (1.33-1.76)	1.37 (1.19-1.58)	1.36 (1.18-1.56)
SGA (<-2 SD below mean birth weight)	1.46 (1.27-1.67)	1.41 (1.23-1.62)	1.39 (1.21-1.59)	1.18 (1.03-1.36)	1.17 (1.02-1.35)
Apgar scores (<7 at 5 minute) [a]	2.13 (1.79-2.54)	2.11 (1.77-2.51)	2.07 (1.74-2.47)	2.05 (1.72-2.45)	2.02 (1.70-2.41)
Fetal venous pH <7.15 at birth [a, b]	1.37 (1.06-1.76)	1.32 (1.03-1.71)	1.33 (1.03-1.72)	1.35 (1.05-1.74)	1.36 (1.06-1.76)
Major congenital anomaly	1.47 (1.29-1.67)	1.48 (1.29-1.69)	1.47 (1.29-1.68)	1.44 (1.26-1.65)	1.44 (1.26-1.64)

[a] available since 2004, [b] gathered selectively by indication, NICU= neonatal intensive care unit, LBW= low birth weight, SGA= small for gestational age, CI=confidence interval

Risk factors for and perinatal outcomes of major depression during pregnancy – a population-based analysis during 2002-2010 in Finland

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Keywords: Childbirth, Depression, Population Register, Register, Socioeconomic Status

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Abstract

Objectives: To identify risk factors for and the consequences (several adverse perinatal outcomes) of physician-diagnosed major depression during pregnancy treated in specialized healthcare.

Design: A population-based cross sectional study

Setting: Data were gathered from Finnish health registers for 1996-2010.

Participants: All singleton births (*n*=511,938) for 2002-2010 in Finland

Primary outcome measures: Prevalence, risk factors and consequences of major depression during pregnancy

Results: Among 511,938 women, 0.8% experienced major depression during pregnancy, of which 46.9% had a history of depression prior to pregnancy. After history of depression the second strongest associated factor for major depression was fear of childbirth, with a 2.6-fold (adjusted odds ratio (aOR=2.63, 95% confidence interval (CI)=2.39-2.89) increased prevalence. The risk profile of major depression also included adolescent or advanced maternal age, low or unspecified socioeconomic status (SES), single marital status, smoking, prior pregnancy terminations, anaemia and gestational diabetes regardless of a history of depression. Outcomes of pregnancies were worse among women with than without major depression. The contribution of smoking was substantial to modest for small for gestational age newborn (< -2 standard deviation below mean birth), low birth weight (< 2,500 g), preterm birth (<37 weeks) and admission to neonatal intensive care associated with major depression was, whereas SES made only a minor contribution.

Conclusions: Physician-diagnosed major depression during pregnancy was found to be rare. The strongest risk factor was history of depression prior to pregnancy. Other associated factors were fear of childbirth, low SES, lack of social support and unhealthy reproductive behavior such as

smoking. Outcomes of pregnancies were worse among women with than without major depression. Smoking during pregnancy made a substantial to modest contribution to adverse outcomes associated with depression during pregnancy.

Key words: Childbirth, Population Register, Depression, Register, Socioeconomic Status

Article summary

Article focus

- To identify risk factors for and the consequences of physician-diagnosed major depression during pregnancy defined according to the International Classification of Diseases (ICD) - 10 codes during pregnancy.

Key messages

- After history of depression prior to pregnancy the strongest associated factor for major depression during pregnancy was physician-diagnosed fear of childbirth.

- Outcomes of pregnancies were worse among women with than without major depression.

Strengths and limitations

- Strengths of this study were the population-based data gathered from three mandatory national health registers, and physician-diagnosed depression defined by ICD-10 codes.

- Possible limitations were that we did not have information on women diagnosed and treated for major depression during pregnancy in primary health care, information on history of depression was based on outpatient and inpatient visits only since 1998 and 1996, respectively, and we did not have information on antidepressant medication at an individual level.

Introduction

Depression is globally one of the leading causes of disease burden for women.(1) A previous large population-based study reported that 0.8% of 32.2 million women had physician-diagnosed depression at the time of delivery in United States (US) during 1998-2005.(2) A recent systematic review concluded that according to multivariable analyses, life stress, lack of social support and domestic violence were associated with an increased risk of depression during pregnancy, whereas maternal anxiety, history of depression, unintended pregnancy, lack of private medical insurance, low income, low education, smoking, single marital status and poor relationship were only significant predictors in bivariable analysis.(3) The authors of this review highlighted several limitations of previous studies, such as differences in the methods used to screen depression, study population, risk factors and confounders included in statistical analyses. It has been suggested that use of self-reported screening methods may overestimate the prevalence of depression, which in turn suggests that their sensitivity and specificity are not adequate.(4) Further, several previous studies have shown that diabetes mellitus, gestational diabetes,(2,5) preeclampsia,(2,6) anaemia, caesarean section and placental abnormalities(2) are more prevalent among women suffering from perinatal depression.

Antepartum and postpartum depression represent a risk for children's short- and long-term wellbeing.(7) Several studies have reported an association between antepartum depression and risk of preterm birth, but no association with other adverse outcomes, such as low birth weight, admission to a neonatal intensive care unit and low Apgar scores, as shown in a systematic review and meta-analysis.(8) However, many of these studies were potentially underpowered because of small sample sizes and were also heterogeneous with respect to the study population and analyses. Further, the use of different methods to measure and define depression raises questions about whether all studies really measured clinically diagnosed major depression.(8) Further, the previous

mentioned large population-based study from US found that physician-diagnosed depression at the time of birth was associated with an increased prevalence of preterm birth, fetal growth restriction, fetal abnormalities, fetal distress and fetal death.(2)

The aim of the present large population based cross sectional study was to identify risk factors for major depression during pregnancy based on ICD-10 codes (International Classification of Diseases) treated in specialized healthcare units, especially an association between a prior history of depression and antepartum depression that was only studied by few smaller studies.(3) Furthermore, we studied whether major depression during pregnancy was associated with adverse perinatal outcomes and the degree to which this association was attenuated by women's SES and smoking (strongly associated with adverse perinatal outcomes)(9) during pregnancy in Finland. Most previous studies considering an association between adverse perinatal outcomes and depression were small and population based studies were scarce.(8) Further, differences in health care services such as access to antenatal care might limit generalizability of the large previous study from US.(2) In Finland, with around 5.5 million residents, health care services are mainly publicly funded and all women have free access to antenatal care.

Materials and Methods

Data and population

Data were gathered from three national health registers currently maintained by the National Institute for Health and Welfare and were linked using women's encrypted unique personal identification numbers. The Finnish MBR contains demographics, pregnancy and delivery characteristics and diagnoses on all live births or stillbirths delivered after the 22nd gestational week or weighing 500 g or more during the first postnatal week recorded since 1987. The MBR data was supplemented by information on maternal health (major depression, preeclampsia,

gestational diabetes, pre-existing diabetes, and fear of childbirth) gathered and defined based on ICD-10 codes from the Hospital Discharge Register (HDR). The HDR was established in 1969 and contains information on all aspects of inpatient care and outpatient visits in Finnish hospitals. Information on major congenital anomalies (yes or no) was gathered and the Register of Congenital Malformations established 1963. Data included all women with singleton births (*n*=511,938) from 2002-2010; multiple births (*n*=15,767) were excluded because they carry a higher risk of complications. The present time period was chosen since information on depression (i.e., a history of depression prior to pregnancy) was available since 1996 for inpatient visits and since 1998 for outpatient visits.

The National Institute for Health and Welfare approved study plan and use of the data for the study as required by the national data protection legislation in Finland (Reference number 1749/5.05.00/2011).

Variables and definitions

Depression, physician-diagnosed, was defined by ICD-10 codes F31.3, F31.5 and F32-34 and women were grouped into four categories; 1) no major depression during pregnancy, and no history of depression prior to pregnancy, 2) no major depression during pregnancy with a history of depression prior to pregnancy, 3) major depression during pregnancy with no history of depression prior to pregnancy, and 4) major depression during pregnancy with a history of depression prior to pregnancy. Information on major depression was based on outpatient visits (patients without overnight hospitalization) in specialized health care since 1998 and inpatient visits (at least an overnight stay at a hospital) specialized health care since 1996 gathered from the HDR. In Finland, general practitioners and midwives in health care centers provide primary health care such as antenatal care, and specialists in regional and university teaching hospitals provide specialized health care. Health care professionals at both levels are instructed to evaluate the mother's mental

wellbeing as part of all appointments. Parity was categorized as either nulliparous, if women had no prior births, or multiparous, if women had at least one prior birth. The gestational age was estimated based on first- or second-trimester ultrasonography measurements. Mode of delivery was classified as vaginal spontaneous, breech, forceps, vacuum assisted or caesarean section (CS). Smoking habits during pregnancy based on self-reported information was grouped into three categories: non-smoking, quitted smoking during the first trimester, and continued smoking after the first trimester, i.e., smoking. Marital status was classified as either married (including women living with a partner) or single. SES was grouped into five categories based on the Finnish Classification of Occupations(10) which was developed according to international recommendations: upper white-collar workers, such as physicians and lawyers; lower white-collar workers, such as nurses and secretaries; blue-collar workers, such as cooks and cashiers; others; and missing information, as categorized and published elsewhere.(11) 'Others' comprised 25.9% (*n*=132,391) of all cases and included all births with unspecified occupations, such as entrepreneurs, students, retired, unemployed and housewives. The category with missing SES information comprised 17.4% (*n*=89,041) of all births. Information on prior CS, induction, miscarriages and pregnancy terminations was dichotomous (yes or no). Information on in vitro fertilization (IVF) included intracytoplasmic sperm injection and frozen embryo transfers. Anaemia was defined as hemoglobin levels ≤100 g/L. Placenta praevia (O44), placental abruption (O45), preeclampsia (O14 and O15), gestational diabetes (O24.4), and maternal preexisting diabetes (O24.0 and O24.1) were gathered from the HDR based on ICD-10 codes. Fear of childbirth was defined by national ICD-10 code O99.80. Feelings towards childbirth are asked all women in antenatal care and women experiencing significant fear of childbirth that cannot be counseled during antenatal visits in primary health care or making CS request due to fear of childbirth are referred to specialist maternity care as described previously.(12,13)

Adverse perinatal outcomes: Admission to a neonatal intensive care unit (NICU) was defined as at least 24 hour surveillance at neonatal intensive care. Stillbirth was defined as fetal death from 22 gestational weeks onwards or birth weight 500 grams or more and early neonatal death as death during the first seven postnatal days. Preterm birth was defined as gestational age < 37+0 weeks. Low birth weight (LBW) was defined as a birth weight of less than 2,500 grams. Small for gestational age (SGA) was defined as a sex- and parity-specific birth weight more than two standard deviation (SD) below the mean weight for gestational based on the national 2013 population-based reference.(14) Five minute Apgar scores < 7 and infant's vein pH < 7.15 were considered low (taken by indication and both available since 2004).

Statistical analyses

Differences between the four categories of women defined by their depression history as described previously were evaluated by chi-square test for dichotomous or categorical variables and Kruskal-Wallis test for continuous variables. Unadjusted and adjusted odds ratios (ORs) of major depression were determined by using logistic regression analyses. The outcome event of interest was major depression during pregnancy (categories 3 and 4), and the reference group was all women without major depression without or with a history of depression prior to pregnancy (categories 1 and 2). All covariates were determined based on literature and results of bivariable analyses.

To address the second research aim regarding the contribution of major depression to adverse perinatal outcomes with or without further control for smoking, SES and other covariates, a second set of logistic models was fitted. For each perinatal outcome, a preliminary model (Model 1) was used to estimate the association between major depression and perinatal outcome. Then, additional covariates were added in subsequent models: adjustment for age and parity (Model 2), adjustment for Model 2 variables plus SES (Model 3), adjustment for Model 2 variables plus smoking (Model 4), and adjustment for all variables simultaneously (Model 5). Furthermore, multiple imputations

were performed to study whether missing information on SES affected our results of logistic regression analysis. The data were analyzed using SPSS for Windows 19.0, Chicago, IL. Differences were deemed to be significant if $p < 0.05$. In addition, 95% confidence intervals (CIs) were calculated.

Results

In total, 0.8% (*n*=4,120) of 511,938 women with singleton pregnancy suffered from major depression during pregnancy as diagnosed by ICD-10 codes in specialized healthcare units. Of all the women with major depression during pregnancy, 53.1% (2,189 of 4,120) did not have a history of depression prior to pregnancy. Table 1 shows demographics, delivery characteristics and reproductive factors for women with and without major depression during pregnancy according to their history of depression prior to pregnancy. Women who suffered from major depression during pregnancy were more frequently nulliparous, younger, and gave birth by caesarean section, to a male infant, and had a lower mean birth weight compared with women with no depression during pregnancy. Further, they more frequently were smokers, of unspecified SES and had reproductive risk factors, such as prior pregnancy terminations, anaemia, major congenital anomalies, gestational diabetes and maternal pre-existing diabetes, and suffered more frequently from fear of childbirth compared with women with no major depression during pregnancy.

Table 2 shows risk factors for major depression during pregnancy (categories 3 and 4) using women with no major depression without or with a history of depression prior to pregnancy (categories 1 and 2) as a reference population. The strongest risk/associated factors for major depression during pregnancy were a history of depression prior to pregnancy and fear of childbirth, which were associated with a 22.4- and 2.6-fold increased prevalence of major depression during pregnancy, respectively. An increased prevalence of major depression during pregnancy was also associated with adolescent and advanced maternal age, smoking during pregnancy, single marital status, prior

pregnancy terminations of pregnancy, low or unspecified SES, anaemia and gestational diabetes. We performed all the analyses using multiple imputed data, but the results did not change (data not shown).

Pregnancies of women who suffered from major depression during pregnancy more frequently resulted in adverse perinatal outcomes, such as, stillbirth, preterm birth, LBW, SGA, Apgar scores < 7 at 5 minute, fetal venous pH < 7.15 at birth, admission to a neonatal intensive care unit and major congenital anomalies, compared with women without major depression during pregnancy (Table 3). Major depression was not associated with early neonatal death. Smoking appeared to contribute the most to the increased prevalence of SGA, LBW, preterm birth, stillbirth and admission to a neonatal intensive care associated with major depression, but made only a minor contribution to the increased prevalence of other perinatal outcomes, except early neonatal death and low fetal venous pH, associated with major depression during pregnancy. SES made a minor contribution to the increased prevalence of all perinatal outcomes, except admission to a neonatal unit, early neonatal death and low fetal venous pH, associated with major depression during pregnancy.

Discussion

Main findings

The prevalence of major depression during pregnancy among women with singleton births was 0.8%, which is consistent with a previous population- and diagnosis-based study,(2) but substantially lower than 3.1-12.8% reported by smaller studies utilizing mostly self-reported screening or interviews.(15-17) This finding is likely to indicate that self-reported screening methods such as the Edinburg Depression Scale (EDPS) are likely to be sensitive to early mental

health concerns and may overestimate prevalence of depression.(18) Furthermore, self-reported screening methods are not adequate to predict only depressive symptoms; they are suggested to be sensitive also for anxiety and stress-related symptoms.(4,18) More than half of the depression episodes occurred in women without a history of depression prior to pregnancy. The second strongest associated factor for major depression during pregnancy after history of depression was fear of childbirth, which was associated with three-fold increased odds of major depression during pregnancy. Major depression during pregnancy occurred most frequently in women with low or unspecified SES, single marital status and unhealthy behavior, such as smoking. Outcomes of pregnancies in women with major depression were substantially worse than in women with no major depression during pregnancy. Smoking during pregnancy contributed substantially to an increased prevalence of SGA, LBW, preterm birth and admission to a neonatal unit associated with major depression during pregnancy.

Strengths and limitations

The present study has several strengths: the data included the entire childbearing population gathered from three national health registers with high-quality data(19,20) depression during pregnancy was diagnosed by a physician, and some novel risk factors, such as fear of childbirth, were studied. However, we acknowledge several limitations with the present study. Information on depression covered only cases diagnosed and treated in specialized medical care units. We did not have information on women experienced major depression during pregnancy diagnosed treated in primary health care. However, it is likely that most high-risk pregnancies such as women with diagnosed depression were treated in by specialized maternity care, thus providing us information on most women with major depression. Further, information on depression was available only since 1996 for inpatient visits and since 1998 for outpatient visits, and therefore we may not have had complete information on all pre-pregnancy depression episodes. It is also of note that maternal

perinatal mental health is influenced by several factors such as parental relationship (such as domestic violence), substance abuse, and personal characteristics not studied in the present study. It has been suggested that depressive, anxiety and stress-related symptoms are much more common than doctor diagnosed disorders such as depression and anxiety.(4,18) However, we did not have information on all possible confounders and other maternal mental health concerns such as anxiety and stress-related diagnosed disorders. In addition, we had no information on antidepressant medication at an individual level and history of adverse pregnancy outcomes, and thus could not assess their roles as confounders in the multivariable analyses. Further, information on SES could not be defined or was missing for approximately 40% of the births. SES is self-reported and optional, and due to confidentiality concerns, some women chose not provide it. However, the socio-demographics (such as smoking, maternal age, and parity) of this group were close to those of the general population, and multiple data imputations of missing information did not change the results (data not shown). Further, SES was solely defined based on maternal occupation at birth that is related to education and income in Finland, and is an appropriate available indicator for studies on socioeconomic health disparity.(21,22) Further, due to data protection issues we did not have information on spouses' SES. No adjustment was made for multiple comparisons, and model results should be interpreted accordingly.

Interpretation

History of depression prior to pregnancy was the strongest predisposing factor for major depression during pregnancy. However, more than half of the women with major depression during pregnancy had no history of depression indicating that the first episode of depression is not uncommon during pregnancy. A previous systematic review(3) did not report a positive association between a history of depression prior to pregnancy and antenatal depression, but there were only three studies with multivariable analyses. The three previous studies were with small sample size and had

heterogeneity in assessment for a prior history of depression.(3) A novel finding of the present study was that physician-diagnosed fear of childbirth was associated with on the order of three-fold increased prevalence of major depression during pregnancy. Several previous studies reported an association between anxiety disorders and major depression during pregnancy as previously reviewed.(3) We showed also that low SES, lack of social support, and unhealthy reproductive behavior, such as smoking, were risk factors for major depression during pregnancy. These results are partly in line with a previous systematic review suggesting that smoking, anxiety symptoms, lower SES, life stress, and lack of social support were associated with an increased prevalence of antepartum depression.(3) Further, the association between gestational diabetes and maternal pre-existing diabetes was in accordance with the results of previous studies.(2,5) However, our results did not confirm the association between preeclampsia and perinatal depression found in previous studies.(2,6) In general, it has been suggested that depression and other pregnancy morbidities, such as diabetes and preeclampsia, would have a partially common physiological pathway.(23) Risk factors for major depression during pregnancy did not vary substantially between women with and without a history of depression (data not shown).

Our results showed that outcomes of pregnancies affected by major depression during pregnancy were worse than pregnancies not affected by major depression during pregnancy. Several previous studies reviewed found a positive association between preterm birth and depression during pregnancy, but not with other outcomes such as LBW, Apgar scores and admission to NICU.(8) However, the authors suggest that the results might be affected by differences in definition of perinatal outcomes (many studies did not use standard definitions), and that many studies were underpowered or did not have all important covariates such as maternal smoking.(8)

Adverse perinatal outcomes are strongly associated with SES and health behavior such as smoking. (9) In the present study it seemed that smoking mediated the association between adverse perinatal

outcomes and depression during pregnancy. However, whether there is causation between smoking and depression and how these are linked, i.e., whether depression leads to smoking or smoking alters the risk of depression, could not be fully evaluated in the present setting; thus exact meditational analyses were not conducted. Based on previous systematic reviews and meta-analysis, antidepressant medication during pregnancy has been shown to be associated with preterm birth,(24) lower Apgar scores,(24) and poor neonatal adaptation,(25) but not with major congenital anomalies.(26) Further, exposure specifically to SSRIs has been shown to be associated with preterm birth,(27) and low Apgar scores,(28) but not with stillbirth, neonatal mortality or postnatal mortality.(29) A limitation in the present study was that we could not assess the contribution of antidepressant medication to adverse perinatal outcomes associated with depression during pregnancy, since we did not have access to this information on an individual level. Among the total delivering population, the use of selective serotonin reuptake inhibitors (SSRIs) ranged from 0.5% in 1997 to 3.7% in 2010 in Finland.

Conclusions

Using a large nine-year national population-based data on all singleton births, we concluded that physician-diagnosed episodes of major depression in specialized healthcare units during pregnancy were rare. Maternal perinatal mental health is a complex issue and influenced by several psychosocial factors, and it has been shown that depressive, anxiety and other stress-related symptoms measured by self-reported screening, not studied in the present study, have been suggested to be much more common than diagnosed disorders such as perinatal depression. The strongest risk factor for major depression was history of depression prior to pregnancy. This result may help clinicians to recognize the risk of depression. Other risk factors for major depression during pregnancy were low SES, lack of social support and unhealthy behavior during pregnancy, such as smoking. Major depression was also associated with fear of childbirth. Outcomes of

pregnancies among women affected by major depression during pregnancy were worse than in unaffected women, but smoking during pregnancy made a substantial or modest contribution to the increased prevalence of SGA, LBW, preterm and admission to a neonatal unit associated with depression during pregnancy. Furthermore, its of note that women with history of depression prior to pregnancy or major depression during pregnancy are more likely to experience postpartum depression,(30,31) and consequences of postpartum depression might be more severe for women, since it has shown to be associated with an increased risk of self-harm such as suicide.(32,33) Therefore, because of possible severe maternal and fetal consequences and high risk of relapse, treatment of antepartum depression should be managed actively by a multi-professional team.

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Data sharing: No additional data available.

Contributor statement

All authors participated in designing the study. SR managed the dataset and performed statistical analyses. SML, HSN, MG, MRK and SH were statistical advisors. All authors contributed to the interpretation of the results, as well as to writing and editing the manuscrip

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Table 1. Delivery characteristics and reproductive risk factors among women with singleton pregnancies with and without major depression during pregnancy and with and without a history of depression prior to pregnancy from 2002 to 2010 in Finland.

Characteristic	No major depression during pregnancy, *n*=493,037 (96.3%)	No major depression during pregnancy, *n*= 14,781 (2.9%)	Major depression during pregnancy, *n*=2,189 (0.4%)	Major depression during pregnancy, *n*=1,931 (0.4%)	*p value**
A history of depression prior to pregnancy	No	Yes	No	Yes	
Nulliparous % Multiparous	42.0 58.0	45.1 54.9	45.5 54.5	50.0 50.0	*≤0.001*
Mean maternal age, years (SD)	29.6 (5.4)	27.6 (6.0)	28.4 (6.2)	28.7 (6.6)	≤0.001
Mean gestational age, wk (SD)	39.8 (1.8)	39.7 (1.9)	39.4 (2.0)	39.5 (2.0)	≤0.001
Mode of delivery % Vaginal spontaneous Breech Forceps Vacuum assistance Caesarean section	 75.8 0.6 0.1 7.2 15.9	 74.8 0.6 0.1 7.5 17.1	 72.6 0.2 0.1 7.5 19.6	 70.4 0.4 0.0 7.7 21.5	≤0.001
Mean birth weight, g (SD)	3531.4 (550)	3479.0 (568)	3453.1 (580)	3456.3 (608)	≤0.001
Male fetal sex %	51.2	50.0	51.1	51.8	0.04
Major congenital anomalies %	4.0	5.2	5.6	5.9	≤0.001
Smoking status % Non-smoking Quit smoking during 1st trimester Smoking after 1st trimester Missing information	 83.2 3.7 10.5 2.6	 63.4 6.9 26.7 2.9	 66.1 6.5 25.1 2.3	 59.5 8.3 29.3 3.0	≤0.001
Married or living with a partner %	93.5	86.3	83.1	83.0	≤0.001
Socioeconomic status % Upper white-collar worker Lower white-collar worker Blue-collar worker Others [a] Missing information	 8.6 34.5 14.2 25.7 17.2	 3.7 25.8 16.0 31.0 23.6	 4.0 27.9 14.9 31.9 21.3	 3.8 25.5 15.3 30.0 25.3	≤0.001
Prior miscarriages %	20.7	23.6	23.3	23.2	≤0.001
Prior terminations %	12.2	22.4	19.8	21.7	≤0.001
In vitro fertilization (IVF) %	1.6	1.2	0.9	1.3	≤0.001
Anaemia, ≤100 g/L %	1.6	2.6	3.5	2.8	≤0.001
Placenta praevia %	0.3	0.2	0.2	0.4	0.54

Placental abruption %	0.3	0.4	0.5	0.7	0.07
Preeclampsia %	1.2	1.3	0.9	1.2	0.52
Gestational diabetes %	11.2	13.4	14.5	17.6	≤0.001
Pre-existing diabetes %	8.4	10.9	11.6	13.6	≤0.001
Prior caesarean section %	10.6	10.5	10.3	10.2	0.90
Fear of childbirth %	4.6	11.4	15.0	17.5	≤0.001

SD=standard deviation, *chi-square or Kruskal-Wallis test, [a] 'Others' comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases,

Table 2. Unadjusted and adjusted odds ratios (aOR) of major depression during pregnancy among women with singleton pregnancies from 2002-2010 in Finland using women with no major depression during pregnancy without and with a history of depression prior to pregnancy as a reference population (categories 1 and 2).

Characteristic	Unadjusted OR (95% CI)	*Adjusted OR (95% CI)
A history of depression prior to pregnancy	29.43 (27.62-31.35)	22.36 (20.86-23.98)
Maternal age (years)		
≤19	3.14 (2.79-3.52)	1.58 (1.38-1.81)
20–29	1	1
30–39	0.86 (0.81-0.92)	1.19 (1.11-1.28)
≥40	1.41 (1.22-1.63)	1.65 (1.41-1.94)
Nulliparous women	1.25 (1.18-1.33)	1.21 (1.12-1.30)
Multiparous women	1	1
Smoking status		
Non-smoking	1	1
Quit smoking during 1st trimester	2.52 (2.23-2.84)	1.57 (1.38-1.80)
Smoking after 1st trimester	3.25 (3.03-3.49)	1.67 (1.53-1.81)
Missing information	1.32 (1.09-1.60)	1.09 (0.88-1.35)
Married/living with a partner	1	1
Single	2.86 (2.62-3.11)	1.63 (1.48-1.79)
Socioeconomic status		
Upper white-collar worker	1	1
Lower white-collar worker	1.69 (1.43-1.99)	1.42 (1.20-1.69)
Blue-collar worker	2.29 (1.93-2.73)	1.53 (1.27-1.84)
Others [a]	2.59 (2.20-3.05)	1.67 (1.40-1.98)
Missing information	2.88 (2.43-3.40)	1.66 (1.39-1.98)
Prior miscarriages	1.15 (1.07-1.24)	1.09 (1.00-1.18)
Prior terminations	1.82 (1.69-1.97)	1.14 (1.04-1.24)
In vitro fertilization (IVF)	0.70 (0.53-0.94)	0.78 (0.58-1.07)
Anaemia ≤100 g/L	2.02 (1.70-2.41)	1.49 (1.22-1.81)
Gestational diabetes	1.49 (1.37-1.62)	1.29 (1.11-1.50)
Pre-existing diabetes	1.56 (1.42-1.71)	1.10 (0.93-1.31)
Fear of childbirth	3.80 (3.49-4.13)	2.63 (2.39-2.89)
Male fetal sex	1.01 (0.95-1.07)	0.97 (0.91-1.04)

*ORs of major depression adjusted by history of depression prior to pregnancy, maternal age, parity, smoking status, marital status, SES, prior miscarriages, prior terminations, IVF, anaemia, gestational diabetes, pre-existing diabetes, fear of childbirth, and fetal sex.

[a] Others comprise entrepreneurs, students, retired women, unemployed women, housewives and all unclassifiable cases, CI=confidence interval

Table 3. Adjusted odds ratios (ORs) of major depression during pregnancy associated with adverse perinatal outcomes among singleton births in Finland from 2002-2010.

Perinatal outcome	**Model 1** adjusted by major depression during pregnancy	**Model 2** adjusted by Model 1 + age and parity	**Model 3** adjusted by Model 2 + socioeconomic status (SES)	**Model 4** adjusted by Model 2 + smoking	**Model 5** adjusted by Model 2 + SES and smoking
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Admission to a NICU	1.79 (1.65-1.95)	1.78 (1.64-1.94)	1.78 (1.64-1.93)	1.68 (1.55-1.83)	1.69 (1.55-1.84)
Stillbirth	1.97 (1.33-2.93)	2.01 (1.35-2.99)	1.86 (1.25-2.76)	1.88 (1.27-2.80)	1.77 (1.19-2.63)
Early neonatal death	1.08 (0.49-2.42)	1.13 (0.50-2.51)			
Preterm birth (<37 weeks)	1.57 (1.39-1.77)	1.57 (1.39-1.77)	1.55 (1.37-1.75)	1.49 (1.32-1.68)	1.48 (1.31-167)
LBW (<2500 grams)	1.56 (1.36-1.79)	1.55 (1.35-1.79)	1.53 (1.33-1.76)	1.37 (1.19-1.58)	1.36 (1.18-1.56)
SGA (<-2 SD below mean birth weight)	1.46 (1.27-1.67)	1.41 (1.23-1.62)	1.39 (1.21-1.59)	1.18 (1.03-1.36)	1.17 (1.02-1.35)
Apgar scores (<7 at 5 minute) [a]	2.13 (1.79-2.54)	2.11 (1.77-2.51)	2.07 (1.74-2.47)	2.05 (1.72-2.45)	2.02 (1.70-2.41)
Fetal venous pH <7.15 at birth [a, b]	1.37 (1.06-1.76)	1.32 (1.03-1.71)	1.33 (1.03-1.72)	1.35 (1.05-1.74)	1.36 (1.06-1.76)
Major congenital anomaly	1.47 (1.29-1.67)	1.48 (1.29-1.69)	1.47 (1.29-1.68)	1.44 (1.26-1.65)	1.44 (1.26-1.64)

[a] available since 2004, [b] gathered selectively by indication, NICU= neonatal intensive care unit, LBW= low birth weight, SGA= small for gestational age, CI=confidence interval

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
D **Title and abstract**	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **OK**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **OK**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **OK**
Objectives	3	State specific objectives, including any prespecified hypotheses **OK**
Methods		
Study design	4	Present key elements of study design early in the paper **OK**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **OK**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **OK**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **NA**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **OK**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **OK**
Bias	9	Describe any efforts to address potential sources of bias **OK**
Study size	10	Explain how the study size was arrived at **TOTAL POPULATION**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **OK**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **OK**
		(*b*) Describe any methods used to examine subgroups and interactions **OK**
		(*c*) Explain how missing data were addressed **OK**
		(*d*) If applicable, explain how loss to follow-up was addressed **NO**
		(*e*) Describe any sensitivity analyses **OK**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **OK**
		(b) Give reasons for non-participation at each stage **NO**
		(c) Consider use of a flow diagram **NA**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **OK**
		(b) Indicate number of participants with missing data for each variable of interest **OK**
		(c) Summarise follow-up time (eg, average and total amount) **OK**
Outcome data	15*	Report numbers of outcome events or summary measures over time **OK**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were

		adjusted for and why they were included **OK**
		(*b*) Report category boundaries when continuous variables were categorized OK
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **OK**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **OK**
Discussion		
Key results	18	Summarise key results with reference to study objectives **OK**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **OK**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **OK**
Generalisability	21	Discuss the generalisability (external validity) of the study results **OK**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **OK**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.